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Commission of Inquiry on the Blood System in Canada

**Interim Report
Annexes**



Commission of Inquiry on the Blood System in Canada



**Interim Report
Annexes**



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Canada



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ANNEX I



Commission of Inquiry on the Blood System in Canada

**REPORT OF THE MANAGEMENT COMMITTEE
NOVEMBER 1994**

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Executive Summary

To assist the Commissioner in preparing his Interim Report on Safety of the Blood System in Canada, a Management Committee was established in the spring of 1994. The objective of the committee was to assess safety of the present blood supply and to make recommendations on ways to minimize risks and continuously improve the safety of the blood system. This study is concerned with the blood system in 1994; its scope **does not** include the past system, especially events occurring during the 1980s. Conducted at a time when the Canadian blood system is undergoing considerable change and has attracted much public attention, the study provides a "snapshot" during this period of transition.

The Management Committee was composed of 10 individuals with expertise in various disciplines relevant to understanding the complexities of the blood system. The committee's approach covered three areas:

1. A review of data concerning the current frequency of transmissible disease markers in blood and blood products in Canada
2. A review of present practices at the regional blood centres, including standards of operation and the likelihood that errors will lead to adverse health effects in recipients of blood and blood products
3. A review of the way the blood system operates in Canada, in order to assess its ability to provide and maintain a safe and secure supply of blood and blood products.

The committee met on eight occasions between March and November 1994. Meetings were also held with senior executives from the Canadian Red Cross Society (CRCS) National Office, Bureau of Biologics (BoB), and the Canadian Blood Agency (CBA) and with clinicians and technologists who use blood and blood products. Site visits and detailed inspections of regional blood centres, the National Testing Laboratory of the CRCS and the Bureau of Biologics were conducted or commissioned by the committee.

On the basis of these reviews the committee assessed the implications for the safety of the blood system as a whole, for its various subsystems, and for recipients of blood and blood products.

Throughout its review, the committee could not find data from specific studies or other evidence to indicate that the Canadian blood system in 1994 is any less safe than blood systems in other developed countries. However this conclusion is made with the caveat that there are incomplete data on outcomes from use of blood and blood products. In the absence of specific outcome studies in Canada (or any other country), assumptions about safety are based primarily on studies of infectious agents in donations and effective use of screening tests for these infectious agents. In the Canadian system, data on donations and screening tests used do not suggest an increased risk to recipients of blood or blood products in Canada in 1994 compared to other developed countries.

In addition, the committee evaluated whether blood collection, manufacturing and product management operations at regional centres were of a standard to minimize risk of processing errors. The manufacturing practices and control systems were assessed during site visits and detailed centre inspections. The overall assessment was that the systems in place were satisfactory yet fragile. This overall assessment was made taking into consideration the ability of the well-trained, meticulous and dedicated staff to cover the deficiencies identified.

Without being rectified, the deficiencies identified could seriously compromise safety. The committee's analysis led to the following recommendations.

Utilization

Recommendation 1. Eliminate over-utilization of blood and blood products. Blood and blood products should be used only when clearly indicated.

Studies indicate that a major reduction can be achieved in the utilization of blood and blood products. Elimination of inappropriate use, according to established clinical guidelines, offers the greatest potential for enhancing safety in the system by significantly reducing public exposure to all transfusion-associated risks (known and unknown).

Governance

Recommendation 2. The Canadian blood system must be restructured to eliminate conflicts among the participants, and at the same time clearly define responsibilities for the safety of the blood supply and for the operations of the blood subsystem.

The committee found evidence of major problems with the current governance. The structure does not clearly focus

responsibilities and relationships. Moreover, the Canadian Blood Agency and the Canadian Red Cross Society are adversarial.

Regulation

Recommendation 3. The Bureau of Biologics (BoB) must take a leadership role in assuring safety of the blood supply. The BoB must be provided with sufficient resources for staff, testing and training to operate effectively.

The Bureau of Biologics is under-resourced and has not taken a leadership role in assuring that safety systems are in place in blood centres. A number of specific deficiencies were identified, such as the need for regulations specifically for blood and blood products, and for ensuring that regulations are strictly enforced through regular, comprehensive inspections with timely follow-up.

Process

Recommendation 4. The Canadian Red Cross Society (CRCS) must continue to implement a strong quality program emphasizing good manufacturing practices and a total quality management approach to ensure continuous process improvement. The CRCS must develop or acquire an integrated computer system that includes a laboratory data management system.

The manufacturing process is essentially in control and managed by dedicated, knowledgeable staff. The CRCS must continue implementing quality programs in each centre. Also, improved planning and management of change are needed in the blood supply system to support process safety in the future. Rapid deployment of an integrated computer system available at each centre must be given high priority.

Donor Issues

Recommendation 5. New systems for donor management are needed to ensure a stable, well-characterized donor base. Given the concentration of transmissible disease risk among first-time donors, implementation of a dual-track system should be evaluated where repeat donors are given routine screening and first-time donors are given more intensive assessment.

Significant improvements in donor management are needed to ensure safety of blood products. Since first-time donations (11% of total) contribute disproportionately to the residual risk from transmissible diseases, it is particularly important to redesign the screening process to differentiate between first-time donors (including infrequent donors) and repeat donors.

Surveillance

Recommendation 6. Comprehensive surveillance is needed to document infection and other adverse outcomes, so that threats to safety of the blood system can be assessed. Mechanisms must be put in place to ensure national reporting, international links, unified responsibility for analysis and clear authority for rapid response to indications of emerging threats to the blood system.

Current mechanisms for surveillance are conducted very much on an ad hoc basis.

Monitoring

Recommendation 7. Monitoring must be improved to include outcome analysis based on full tracking of units from donors through to recipients.

Major deficiencies are evident in the ability of the blood system to monitor outcomes among transfusion recipients and provide adequate follow-up of adverse effects.

Research and Evaluation

Recommendation 8. An ongoing program of health systems, clinical and basic research is needed to ensure continual improvements to the blood system.

Most research related to blood in Canada is investigator initiated and addresses basic medical research questions. Research needs to be directed and expanded to encompass health systems research, including evaluations of strategies, procedures and policies aimed at improving safety and efficiency of the blood system.

Recommendation 9. Concerted action must be taken to rebuild the confidence of the Canadian public in the blood system.

It is not sufficient that the blood system be safe; it must also be considered safe. Public confidence in the Canadian blood system is now so low that it will require significant action to restore it. Together with other measures taken to improve the system, a concerted communication program must be initiated to rebuild public confidence as soon as possible.

The committee's findings can be summarized in the responses to the following three questions:

1. Should Canadians who need blood or blood products have to worry that they are less safe in Canada than in other developed countries?

The answer as far as the committee could assess is no. In 1994, no evidence was identified of increased risk to blood or blood product recipients in Canada compared to that in other developed countries.

2. Can important deficiencies be identified in the Canadian blood system?

The answer is yes. This report provides details regarding a number of deficiencies in the current blood system in 1994.

3. If deficiencies are not corrected, is there significant potential risk to the safety of the Canadian blood supply in future years?

The answer is yes. The recommendations from this study are presented as constructive steps that, when implemented, will assure continual improvement and safety of the Canadian blood system.

PART 1 Approach

1.1 Introduction

The Commission of Inquiry on the Blood System in Canada was established "to review and report on the mandate, organization, management, operations, financing and regulation of all activities of the blood system in Canada."¹ Its mandate included both the organization and effectiveness of past and current systems designed to supply blood and blood products in Canada. Item 6 of the order-in-council states:

6. the Commissioner be directed to submit an interim report in both official languages to the Governor-in-Council no later than May 31, 1994 on the safety of the blood system, with appropriate recommendations on actions which might be taken to address any current shortcomings. (The date was subsequently amended.)

A plan was developed to assist the Commissioner in meeting the above objective and a Management Committee was appointed to execute the plan. This report to the Commissioner describes the Management Committee's process in assessing the safety of the blood supply system, its findings and recommendations for improvements.

1.2 Terms of reference

The terms of reference for the Management Committee were set out in a series of recommendations in a memorandum approved by the Commissioner and dated February 3, 1994 (Appendix I). The recommendations were as follows:

1: The scope of the Interim Report should be limited to matters of safety in the Blood Program of the Canadian Red Cross Society and the work of the regulatory arm of the federal government, the Bureau of Biologics. It may prove to be feasible to formulate some conclusions relevant to the role of the Canadian Blood Agency with regard to safety.

2: Special attention should be given in the review to operational and regulatory procedures which are relevant to the risk of transmission of infectious diseases through therapeutic use of blood and blood products.

3: The review should be based both on examination of documents and site inspections conducted by expert teams.

4: The expert review should include comparison of the Canadian system with those of the United States, the United Kingdom, Australia and New Zealand.

5: Site visits by experts should be made to the central offices of the Bureau of Biologics and the Red Cross, and to some or all of the Regional Centres of the Red Cross.

6: The work of review teams should be supervised by a Management Committee, which should also take responsibility for directing the preparation of a report to the Commissioner on the safety of the system.

7: The Management Committee should be made up of individuals who are leading authorities and who have, collectively, expertise in the following fields: regulation, blood centre management, quality assurance, data systems management, risk management, microbiology and infectious diseases.

8: The Canadian Blood Agency should be invited to submit a brief for review by the Management Committee.

9: The Report of the Management Committee should be released to parties, and comments received, before action is taken by the Commissioner. The Interim Report on Safety of the Blood System should be based on the Report of the Management Committee, on information and views presented by the parties, and on such other sources that the Commissioner believes to be relevant.

It follows from these recommendations that the principal tasks of the Management Committee were to review the present blood system in order to assess safety, and to develop recommendations to minimize risks and integrate mechanisms for continuous improvement in the system.

1.3 Activities of the Management Committee

During February and March 1994, the Commissioner made appointments to the Management Committee in compliance with Recommendation 7, above. The committee held two-day meetings on seven occasions between March and November 1994. The schedule and activities of the committee are summarized in Table 1.

Incorporated in this schedule were:

- orientation visits to Hamilton and Toronto regional blood centres
- meetings with senior executives from the Canadian Red Cross Society (CRCS) National Office, Bureau of Biologics (BoB) and the Canadian Blood Agency (CBA)
- a meeting with clinicians and technologists who are users of blood and blood products.

Table 1

Activities of the Management Committee

DATE	ENTIRE COMMITTEE	SUBCOMMITTEE	OUTSIDE EXPERTS
Mar 2 - 3		Steering committee meeting	
Mar 20 - 22	Committee meeting • Hamilton Centre orientation • Toronto Centre orientation		
Apr 25 - 27	Committee meeting • Meeting with senior officials of CRCS, CBA and BoB • Visit to CRCS National Office, CBA and BoB		
May 25 - 27	Committee meeting • Edmonton site visit • CISCO review		
Jun 13 - 14	Committee meeting		
Jun 29 - 30		Vancouver site visit	
Jul 25 - 27			Review of BoB by John Cash
Jul 28 - 29	Committee meeting		Users meeting
Aug 4 - 5		Halifax site visit	
Aug 18 - 19	Committee Meeting		
Aug 23 - 25			Review of CRCS NTL by Carol Major
Sep 6 - 9			Review of BoB by John Finlayson
Sep 30 - Oct 1	Committee meeting		
Oct 17 - 21			Inspection of Montreal Centre by Martin Bruce and Helen Starr
Oct 24 - 28			Inspection of Saint John Centre by Martin Bruce and Helen Starr
Oct 31 - Nov 4			Inspection of Winnipeg Centre by Martin Bruce and Helen Starr
Nov 6 - 7	Committee meeting • Meeting with Martin Bruce		

Table 2

Reports Commissioned by the Management Committee

APPENDIX	SITE/DATE	REVIEWERS	FUNCTIONS REVIEWED
III	National Testing Laboratory, CRCS Aug 24, 1994	Carol Major Head, HIV Laboratory, Laboratory Services Branch, Ontario Ministry of Health	<ul style="list-style-type: none"> • Transmissible diseases lab • Decisions regarding infectious diseases screening • Decisions regarding purchase of products, such as test kits • Evaluation of products • Quality Assurance Programs • External proficiency programs • Confirmatory testing
IV	Bureau of Biologics Jul 25-27, 1994	Dr. John D. Cash National Medical & Scientific Director, Scottish National Blood Transfusion Service, Scotland	<ul style="list-style-type: none"> • Plasmapheresis regulation process • Current Canadian standards/guidelines on blood collection/component manufacturing • Proficiency testing/kit evaluation • Partnerships with U.S. and other countries • Audit/inspection process • BoB management process
V	Bureau of Biologics Sep 7-9, 1994	Dr. John S. Finlayson Associate Director for Science, Office of Blood Research and Review, Center for Biologics Evaluation and Research, USFDA	<ul style="list-style-type: none"> • Review of files • Licence Applications • Records of BoB's reviews • BoB's responses
VI (A)	Montreal Regional Blood Centre Oct 17-21, 1994	Martin Bruce National Quality Manager, Scottish National BTS, Scotland Helen Starr Specialist GMP Auditor Therapeutic Goods Administration, Australia	All operations of regional blood centre
VI (B)	Saint John Regional Blood Centre Oct 24-28, 1994	Martin Bruce Helen Starr	All operations of regional blood centre
VI (C)	Winnipeg Regional Blood Centre Oct 31-Nov 4, 1994	Martin Bruce Helen Starr	All operations of regional blood centre

Task groups appointed by the committee made site visits to:

- regional blood centres in Edmonton, Vancouver and Halifax
- the National Testing Laboratory of the CRCS
- the Bureau of Biologics: one visit to review the inspection reports and blood components submissions, and a second to review submissions for plasma derivatives

-
- regional blood centres in Montreal, Saint John and Winnipeg (these were detailed inspections).

Table 2 provides a list of the reports commissioned by the committee, the names and titles of the reviewers and the location of the reports in the Appendices.

1.4 Site Visits

Appendix I refers to site visits by experts and gives some indication of the nature of site inspections by review teams to be supervised by the Management Committee (see Appendix I, page 5). The committee distinguished between site visits and detailed inspections or audits. It decided, for the site visits, to assess process controls, ie "mechanisms" to control operations. Included in this assessment was a determination of whether there are systems for self-auditing, whether the processes are in control and whether the changes underway would improve the process controls. Appendix II contains a list of the members, the dates and summaries of the site visits to Edmonton, Vancouver and Halifax.

The committee considered several factors in choosing which centres to visit and the style of the visits. It was noted that the Canadian blood system is in a state of transition. A number of initiatives are underway that affect the operations, and alter the benchmarks against which detailed inspections are conducted. These include the decision to implement current Good Manufacturing Practices (cGMPs), the design and implementation of new Standard Operating Procedures (SOPs), and the development of a major, national information management system: Computer Information System for Centre Operations (CISCO). The centres chosen were at varying stages of either piloting or implementing these initiatives. Regional location and size of centre were also considered.

1.5 Site inspections

Recently, the regional blood centres have been subjected to a number of audits and inspections, including internal centre audits, audits by National Office of the CRCS, inspections by the Bureau of Biologics, and in some cases, by Cutter Biological (a division of Miles Inc.) for fractionation of plasma in the U.S. The Red Cross had decided that the blood collection and plasmapheresis centres should comply with the United States Food and Drug Administration (USFDA) regulations. During the course of the committee's work, the USFDA also began inspecting Canadian regional blood centres. (This was in part due to the arrangement that the CRCS has with Cutter Biological for fractionation of Canadian plasma at a plant in North Carolina.) The reports from these inspections and audits were reviewed by the committee.

The committee's approach to conducting detailed inspections was to assemble a team of experts from different jurisdictions. The choice of criteria to be used for the assessment was based on the need to ensure that the inspections be comprehensive, consistent and documented and would distinguish between requirements critical to assuring safety and those meant to standardize and facilitate management and administration of the system. Checklists were developed from a review of the requirements of the USFDA, the Bureau of Biologics in Canada, the Therapeutics Goods Administration (TGA) in Australia, the World Health Organization (WHO), the European Commission (EC) and Britain. The items for the checklist were chosen to cover the critical control points through all aspects of the operations. Critical control points are the steps in the processes that must be performed correctly to ensure the quality of the end product or service. A more detailed description of critical control points follows in Part 2. International standards for safety and good manufacturing practices were used and are included in Appendix VI.

The committee, concerned that aspects of process controls and management issues would be missed with very specific checklists, drafted several questions for the inspectors. These are included along with the inspection reports in Appendix VI.

1.6 Scope

The scope of the committee's work was based on the recommendations regarding the Interim Report on Safety of the Blood System (Appendix I). It was limited to **assessing the safety of the current blood supply system and planned changes, and did not include reviewing the past**. Although the focus was on the supply of blood rather than utilization, on governance rather than funding, and particularly on the risk of transmission of infectious agents, the committee considered the blood system as a whole. The committee recognized that it is essential to understand how all aspects of the system interact and how decisions are made, on what basis and by whom. In the long term, these factors have as great an impact on safety as specific issues within the operations.

Based on review of the functional model and background material on the Canadian blood system (described in detail in Parts 2 and 3) the committee identified several approaches to its task including: a) consider the governance and regulatory structure to determine whether they are adequate to assure safety for the blood supply, b) start with the management of the actual operations and review the mechanisms for ensuring that operations reach appropriate standards of safety, c) the bottom-up approach which involves looking at all the operational elements of the system that supplies the blood and, d) a systems approach to determine what is needed in any system to assure safety and then review the system in place to assess discrepancies from the ideal. The committee used all four of these approaches.

Recognizing the number of specific operations involved in the process from selecting and screening donors, collecting, testing and processing blood, through to delivering the products to the users, the committee placed emphasis on the processes in place to ensure standardization, documentation and mechanisms to detect errors or inconsistencies. For example, rather than trying to determine whether every unit delivered to the hospital carried minimum risk for transfusion, the task was to determine whether the processes were in place that could reasonably assure minimum risk. This approach of relying on process control mechanisms is particularly important for biological systems, as the extent of variability is much greater than it is for chemical processes.

1.7 Documentary sources

The committee had access to documents assembled by the Commissioner. Among those selected for special scrutiny were testimony and exhibits relating to current safety, reports of inspections of Red Cross regional centres conducted by the Bureau of Biologics, and related correspondence, reports of inspections conducted by the USFDA and reports of internal inspections conducted by the CRCS. Documents dealing with GMPs and SOPs from Canada, the United States, the United Kingdom and Australia were assembled and reviewed. Individual members brought forward scientific and technical literature and reports in their respective fields of expertise.

...

PART 2 Functional model of the Canadian Blood System

The functional model of the Canadian blood system (Figure 1) represents the major elements of the system and their interactions. This functional model represents, without reference to the current organizational structure, what has to be done to enable the flow of blood products from donors to recipients. This model would, in most respects, be applicable to any developed nation.

The model is intended to serve as a frame of reference for evaluation of the Canadian blood system. The model identifies the main elements in the system as well as the links between them. It is important to evaluate not only the effectiveness of the elements but also the effectiveness of the links between them. These links may be the more vulnerable parts of the system.

Eventually universal agreement may emerge on the best form and function of a blood system. For the purpose of this study, it suffices that the model is clear and complete enough to serve as a vehicle for reporting our findings and recommendations. A definition of each element of the model and their main interactions with the other elements follows the description of the model.

For each element of the system, critical control points are identified that are key to the safety of the system. These are the basis of the comprehensive evaluation of the system. This approach is an extension of the "critical control point" approach included in good manufacturing practices. The concept, as applied in this report, brings in higher orders of operation of the blood system, namely governance, direction, planning and design.

The impact of deficiencies at the critical control points will vary depending on both the nature of the deficiency and the functional level within the system. Deficiencies at the process level may lead directly to adverse effects on recipients and must be given appropriate weight. Such deficiencies are often a symptom of a failure at a higher level, which suggest potential for other operating deficiencies to occur. In general, the higher the level of decision making, the greater the potential for deficiencies at critical control points to have serious effects on safety.

FIGURE 1
Functional model of the Canadian blood system

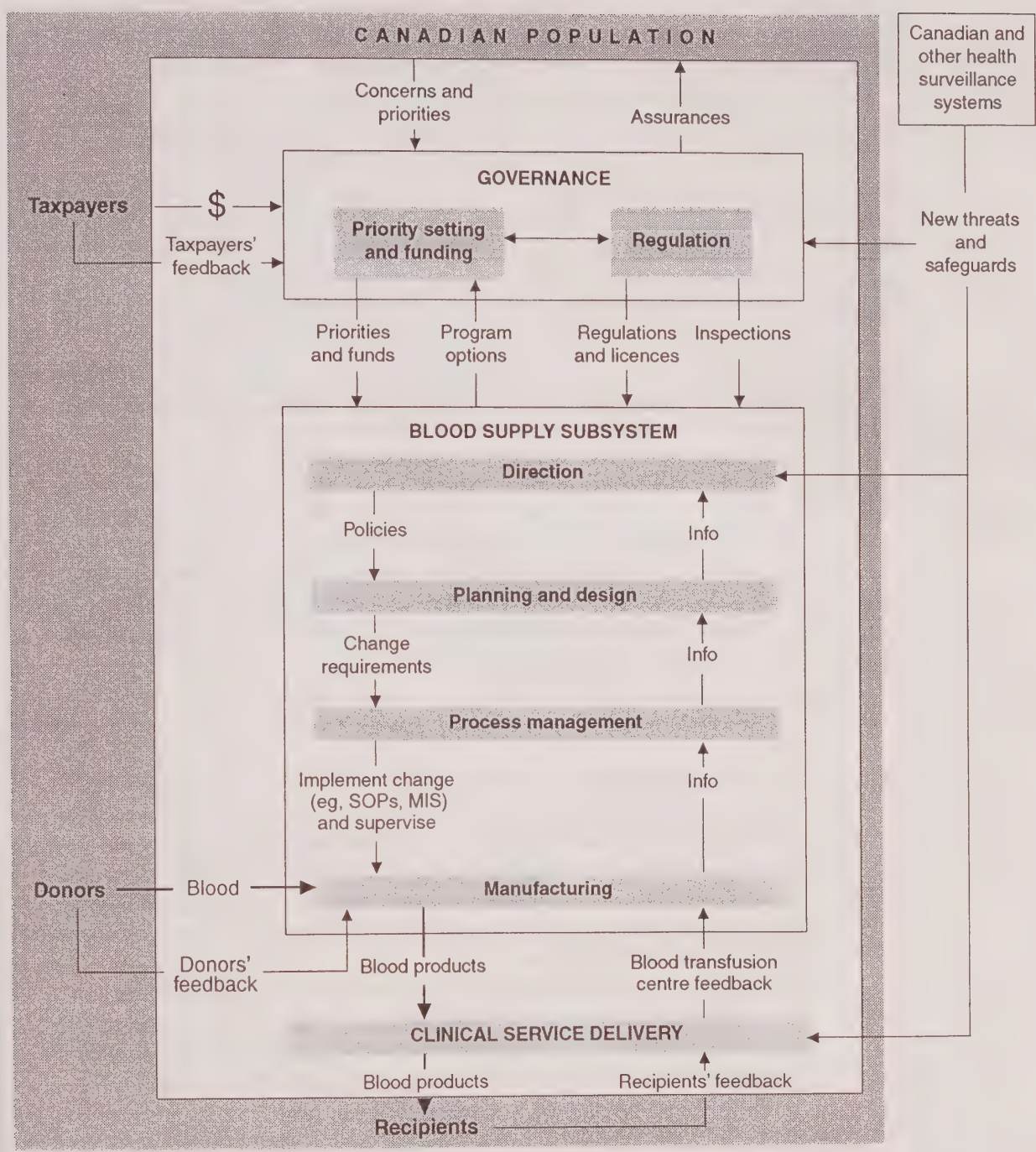


Table 3

Functional levels for quality assurance applied to blood systems

FUNCTIONAL LEVEL	TIME FRAME FOR ACTION	POTENTIAL IMPACT ON SAFETY	EXAMPLE
Direction	decades	general (nationwide)	deciding on self-sufficiency options
Planning and Design	years	general	implementing GMPs, implementing a computer system
Process Management	weeks and months	local or systemic	implementing a new SOP
Process Execution	days	episodic	labelling a unit of blood

2.1 Canadian population

The blood system exists to serve the Canadian people. The people express their concerns and priorities in various ways: elections, polls, action groups, hearings and so on. The Canadian population includes subgroups, such as the taxpayers who currently fund the whole system, blood donors and recipients of blood and blood products.

2.2 Governance

Governance is the act of making decisions on behalf of the Canadian people. It includes two components.

- 1) *Priority setting and funding.* These functions determine what proportion of tax dollars will go to the blood system, and allocates those funds.
- 2) *Regulation.* This function guards the safety of the system by promulgating regulations, granting licences to centres and licensing products, and conducting various types of inspections.

The relationship between these two functions, priority setting and funding, and regulation is delicate and a point of much importance. On the one hand, regulations must operate with a large degree of independence; on the other, regulations are the major influence on the cost/safety balance and must therefore accurately reflect the best interests of the people.

2.2.1 Priority setting and funding

The key elements of priority setting and funding are:

- Representation of blood system needs at higher levels of governance
- Management of blood system priorities and funds
- Crisis management
- Public awareness.

Representation: Because all sectors of our society compete for the same public funds, and because the needs and rules of society are constantly changing, the blood system has to be effectively represented in governance, where priorities and budgets are established. All components of the blood system must work harmoniously to form, at all levels, a coherent, clear picture of the system's needs.

Priorities and funds: The system must have astute, visionary leadership so funds can be allocated where they will be most effective. This requires that the priority setting and funding element of governance be effectively staffed and organized, and that it maintain effective two-way communications with the other elements of the system. Two-way communication in the blood system is a critical control point of the system.

Crisis management: The greatest threats to safety that the system faces are the potentially devastating effects of new problems that may severely compromise the security of the system before they are detected. Because of potential threats, crisis management is a critical element of system safety. Efficient crisis response depends on preparation and readiness. The ability of the system to respond to all types of threats from all directions is a critical control point.

Public awareness: A responsibility of governance is to ensure that the blood system is safe and to provide assurance of safety to the public. The public need to be involved in decisions, understand the risks and have confidence that the system is safe. Public confidence depends not so much on theoretical, calculated safety as on public perceptions. Public confidence is a *key* measure of the system, and the quality of two-way communication with the public is a critical control point.

2.2.2 Regulatory systems

Regulatory programs for blood product collection, processing and distribution include three essential elements:

- development of standards and definition of good manufacturing practices for all portions of the system

-
- review and approval of licence applications for transfusion products and plasma derivatives
 - monitoring of each establishment's compliance with all applicable standards and requirements.

It is most important to have coordination among the three program elements, and for the regulatory authority to have effective tools and adequate resources to enforce standards. The safety of the blood system and the quality of blood products depends not only on the execution of three program elements, but also on the degree to which the standards are communicated to, and understood and implemented by, those being regulated. The workings of the regulatory system should also be transparent to the public.

Development of standards

Because the technical requirements and scientific issues surrounding blood products are constantly changing, the regulatory system must be equipped to re-evaluate continually the existing standards and provide current guidance to all establishments within its span of responsibility. The complex issues related to blood product manufacture today involve many disciplines, so the regulatory system should have access to the necessary expertise that may not always be found within its own small staff. Issues that have significant potential impact should be discussed with all stakeholders in a public forum before policies are established.

Although good manufacturing practices are quite generic, they also require continuing interpretation in light of technical changes and altered manufacturing conditions. A mechanism for rapidly informing all establishments of needed changes in procedures and of potentially serious threats to health is fundamental. Well-established pathways for disseminating new information rapidly and responding to inquiries from all affected parties should extend to every blood establishment, every inspector who monitors compliance, and every reviewer involved in the licence application approval process. It is also useful to ensure that other public health officials involved in blood product safety are kept abreast of changes in requirements for blood collection, processing and distribution.

In an ideal regulatory system, the framework for accomplishing these objectives would include 1) a network for constantly gathering, from all affected parties, information about problems, changes and issues, 2) a core group of decision makers who would meet frequently to address policy issues affecting the standards and their interpretation and 3) a standards publication/dissemination/archiving group who ensure prompt transmittal of all regulatory decisions and related information about interpreting and enforcing regulatory policy.

Licence application review and approval

Establishments applying for blood manufacturing licences or licence amendments for blood or blood products should be given clear guidance on application requirements. The review of applications should follow detailed standard operating procedures that ensure prompt, consistent and thorough review of all information relevant to manufacturing safe and effective blood products. The performance of each establishment/blood centre that will operate under a licence should be documented as part of the review and approval process. If multiple sites will manufacture a new product, the sampling and testing of products for licensure should ensure that all locations produce uniformly good products. The scope of the licence application is most easily defined by implementing a standard format that enables reviewers to determine quickly if all relevant issues have been addressed. The criteria and rationale for approval (and disapproval) should be defined in advance and communicated to applicants as well as reviewers.

In addition, the responsibilities of each participant in the review process and the decision hierarchy should be defined. The agreement or non-agreement of each level of authority in the signature chain should be recorded. Defined procedures are needed for resolving conflicts in a timely manner and making difficult or controversial decisions. Document logging and tracking throughout the review process are essential; established time frames for accomplishing each portion of the review should be considered. A properly responsive regulatory system needs procedures for identifying high-priority applications that may have a major impact on product safety, availability or other aspects of public health.

Monitoring compliance with regulatory requirements

Compliance with regulatory requirements is determined by periodic on-site inspection of each establishment manufacturing blood products. These inspections should be conducted by competent, trained inspectors using a standard format for reviewing operations and recording their observations. Predetermined enforcement action levels for serious violations are needed; defined regulatory sanctions are essential. Following inspections, or the investigation of serious accidents, errors or adverse reactions, the results and findings should be communicated promptly to the establishment involved. It is also important that any broader implications of the occurrence be considered and acted upon if regulatory requirements need revision or safety alerts are appropriate.

There has to be a system for reporting and reviewing adverse reactions as well as errors and accidents. Because some types of serious reactions or product failures may occur only once in a particular location, it is necessary for the regulatory authority to provide a centralized mechanism for recording and analysing such events. For

example, it is difficult to observe trends in transfusion-related fatalities, because they occur at such a low rate. Trends are important for alerting authorities to the emergence of problems that may require regulatory solutions. It is especially important that information from inspections or other compliance programs, such as adverse reaction reporting, be considered regularly as part of the policy development for standards promulgation and review procedures for product licensing.

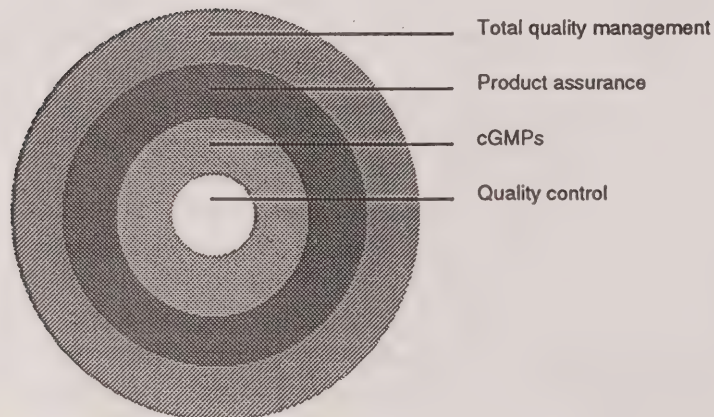
2.3 Blood supply subsystem

2.3.1 Quality management

Blood manufacturing operations are similar in developed countries and include: donor recruitment and screening, collection, testing, component separation, storage and delivery. There is an international trend toward mandating that blood be handled as a drug produced by manufacturers that must be regulated accordingly. As with other drugs, there is a growing international emphasis on GMPs and quality programs. As will be described below, quality programs, although they focus on process controls for operations, also extend into the higher functional levels of the system. They help in forming goals, such as error-free processing and, therefore, also dominate the planning and design function.

FIGURE 2

Quality systems



Total quality management is integrated into a system that includes quality control, GMPs and product assurance. It is an organization's comprehensive system for manufacturing safe, effective, quality products according to regulatory standards, including preventing, detecting and correcting deficiencies that may compromise product quality.

Quality Control is the minimum type of quality program involving inspection and testing of the product. There is limited provision for feedback to design/planning.

Good Manufacturing Practices are broader in scope than quality control and emphasize all aspects of production.

Product Assurance focuses on whether products meet customer requirements and verifies if manufacturing processes are compliant.

Total Quality Management is broader than product assurance, and involves a total shift in the organization's culture to focus on quality in terms of product, customer service, employees and all aspects of the organization's activities.

Each aspect of the process within the blood supply subsystem has critical control points (CCPs), defined as major points in the processes that must be performed correctly to ensure the quality of the end products and services. Items A through I in the list below are "generic" critical control points for any task in the manufacturing process. Many of these generic controls are also applicable to successful implementation of GMPs and total quality management. The linkage between the different functional levels is explicit in critical control point J which reflects a continuous effort to move toward an organization-wide approach to quality and quality management.

Generic Critical Control Points (CCPs) for Process Quality Control

- A. Organizational issues**
- B. Documentation/record keeping/record review**
- C. Education/training/personnel selection**
- D. Validation/calibration/PM/proficiency testing**
- E. Incident/error/accident review**
- F. Process control**
- G. Supplier qualification**
- H. Label control**
- I. Internal assessment**
- J. Process improvement**

Each CCP has associated key elements and system checks that can be monitored to provide assurance that the CCPs are secure and that there is error-free processing

The concept of error-free processing, or zero-defects manufacturing, has value as a long-range objective, since it implies the need for continuous improvement. This concept rejects the idea that efforts can be relaxed short of perfection. The system must be designed so that the CCPs are consistent, reliable and without variation, in order to produce products that meet quality standards.

An organization's ability to produce products or services that meet or exceed specifications and expectations is directly related to the degree to which processes are in control. Process control is directly related to the quality of the people in an organization and the resources they have been given.

2.3.1 Direction

The blood supply subsystem is itself a complete system with four functional levels: 1) direction, 2) planning and design, 3) process management and 4) manufacturing process.

Overall intentions, vision, mission and strategic direction of an organization are formally expressed by senior management. The strategic direction addresses broad, long-term goals in many areas; research and development, investment, marketing, quality management and collection/distribution targets. Important policies are defined and approved at the highest level of the organization. It is at this level that the overall commitment of resources to achieve these broad-based goals is made.

As shown in the functional model, input from governance as well as operations influences the direction-setting process.

2.3.2 Planning and design

The planning and design function formalizes organizational objectives — intended, specific outcomes that are ideally achieved in a relatively short time (in contrast to goals, which are long-term). Based on these objectives, analyses and proposals for major change are prepared and implementation plans developed. Plans may include procedures, programs, processes, product or service specifications and training requirements. Planning and design require that the needs of the customer be known and processes be developed to produce specified products and services consistently and reliably. New technology, manufacturing methodology and donor trends are also part of the process. Planning and design require specific and general tools and will define:

performance features of the end product, cost target, time line, productivity, quality, product development and launch budget.

All operating processes involve some degree of human intervention. Since human performance is subject to various errors due to lapses, mishap, bias or lack of technique, planning and design must include a structured process to focus on reducing human error.

Implementing operations is the final step in planning and design and involves a complete transfer of responsibility. The planning and design function is performed with input from both process management and direction. Communication is two-way.

The critical control point at the planning and design level is the quality of change plans. These plans should be developed with the participation of all levels of the organization and those who will implement them should be involved from the start. These plans should be well aligned to the pursued directions and realistic in terms of budget, timetable, maturity of technology, organization capacity for change and so forth.

2.3.3 Process management

Process management is responsible for the implementation and execution of the plans and the day-to-day supervision of the process itself. This includes the implementation of the quality program, which touches all manufacturing activities. Ongoing, formalized and rigorous self-assessment is a critical tool used by process management and operations.

Process management also actively engages in continuous improvement in all operational processes. Process management and operations will analyse the processes to find ways to attain higher levels of performance. Continuous improvement must be supported organizationally. As indicated in the functional model, the information flow must be two-way between process management and planning and design and between process management and manufacturing.

The commitment and capability of personnel involved in managing the blood supply subsystem to improve quality constantly and maintain a state-of-the-art level of security stands as a critical control point.

2.3.4 Manufacturing process

The process level of the blood supply system is composed of seven major sub-processes as follows: donor screening, blood collection, component processing, testing, review and labelling, storage and distribution and information management. Within each of these stages are critical control points where correct performance is necessary to ensure the quality of the end product or service. The specific critical control points at all levels of the process are presented in Appendix XII. The committee relied on its awareness of these critical control points to plan visits to and audits of the CRCS blood centres.

2.4 Clinical service delivery

Clinical service delivery includes all uses of blood products to treat patients. Since risk increases with use, it is clear that a major critical control point is the proper use of blood products to ensure that they are used only where expected benefits exceed the ever-present risk of blood transfusion and use of blood products.

2.5 Health surveillance systems

The evaluation of safety of the system also depends very much on the performance of health systems in Canada and other countries. Canadian health surveillance systems are not part of the blood system. Their mission should be to monitor all aspects of the health of the Canadian population, including early warning of new pathogens and health history of transfused patients.

The safety of the Canadian blood system also depends on maintaining communications with health surveillance systems in other countries.

PART 3 Canadian Blood System

3.1 Funding

In Canada, the blood program is part of the overall health care system. Therefore, it is funded through the provincial and territorial governments even though it is a national program. The Canadian Blood Agency manages the funding on behalf of the provinces and territories.

3.1.1 Canadian Blood Agency

The Canadian Blood Agency (CBA) is a not-for-profit corporation incorporated in 1991. The members of the corporation are the Ministers of Health in the 10 provinces and two territories. The objectives of the corporation are:

to direct, coordinate and finance the various elements of the Canadian Blood System requiring national direction in accordance with the principles established by the Honourable the Ministers of Health of the Provinces and Territories of Canada for the therapeutic use of human blood, blood products and their substitutes.

Each member appoints a director of the corporation. Decisions are made on a majority vote.

There is no formal contract delegating authority from the Ministers to the CBA. The provinces and territories directed that the funding for the blood program, which is approximately \$250 million, be given to the CBA for disbursement to the Red Cross. The CBA does not have a contract with the Red Cross, nor is there legislation to allow the CBA to dictate the manner in which the Red Cross should operate. However the CBA does have the power to withhold funds.

The principles cited in the CBA's statement of objectives are the seven principles of the blood program approved by the Ministers in 1989 (Appendix XI). The CBA considers that it should have a leadership role, strongly represent the members' interests and be creative and innovative. It sees its mandate as administering the national program with a business-like approach and satisfying the seven principles, but without involvement in the day-to-day operational matters.

William Dobson, the executive director of the CBA, in his testimony to the Commissioner in March 1994, described the CBA directional plan as including:

- **funding:** blood transfusion system, fractionation, and plant and equipment. The CRCS has been given a global budget for the transfusion system since 1992/93,

and the provinces share the cost on the basis of individual consumption of red blood cells. However capital projects are funded, at present, by the provinces, who lease them to the CBA, who leases them to the CRCS. Fractionation products, including high-purity and recombinant products, are billed to the province and it is up to each province which they choose to buy.

- **logistics and distribution:** eg, assessing whether 17 regional centres are still justified.
- **utilization:** ensuring that the use of blood products is effective and follows a medically justified protocol. The CBA is in the process of developing guidelines for the use of products, to advise doctors of differences in consumption patterns and provide educational programs to the medical community.
- **research:** needing to be conversant with worldwide trends. The CBA believes that it should have a say in the national research conducted by the CRCS when the funding is from the provincial or federal governments.
- **quality assurance and risk management:** The CBA acknowledges the controversial nature of such a role, but claims that it has a high level of interest in safety. The CBA proposed that the CRCS be asked to submit quality assurance reports. Recently the CBA established a working group on safety to consider this proposal, among other things. The membership of the group includes the CRCS, Bureau of Biologics, Canadian Hemophilia Society, CBA and the Laboratory Centre for Disease Control, as well as others with expertise in hospital utilization and ethics. The working group is intended to provide the interagency communication that is considered particularly important since an early detection system is not in place. The goal is to identify emerging pathogens or other threats in the blood system as early as possible in order to contain these threats, and to identify each member's mandate in the area of safety.
- **policy:** such as for autologous and directed donations.
- **fractionation:** The Deputy Ministers' Task Force asked the CBA to assume responsibility for negotiating contracts to purchase fractionated products.² CBA formally had a fractionation committee, which called for and received proposals for a fractionation facility in Canada.

It is of interest to note that principle four of the seven principles of the blood program is "Safety of all blood components and plasma should be paramount." CBA believes that this principle is subject to a cost/benefit test. As William Dobson testified, "The concern for safety must be balanced with cost effectiveness and cost efficiency."

The CBA has a number of other committees, including a Scientific Advisory Committee, which consists of eight physicians external and advisory to the Board of Directors. The primary concerns of this committee are utilization and safety. Consideration of the issue of testing for hepatitis B core antigen is an example of its

activities. The BoB was contemplating the introduction of the test. The Scientific Advisory Committee organized a conference on September 2, 1993 of leading experts in North America. The consensus of the conference was that hepatitis B core testing would not add significantly to the safety of the blood system. This decision was communicated to the BoB.

The CBA must approve a new product before it will agree to fund it. An example of this was Alpha IX SD, which is a high-purity factor IX. In 1993, this product had not been approved by the BoB. Physicians were requesting it and the Red Cross was distributing the product for use under the Emergency Drug Release program. The BoB reviews the safety as well as purity, potency and efficacy of a product, but the CBA also considers the cost and the expected medical benefits of a new product. In other words, if it is replacing a drug, the CBA assesses whether the new drug is more efficacious. On such issues the CBA consults its Scientific Advisory Committee.

In a submission that William Dobson made to the committee on April 25, 1994, he described the CBA's role in safety, noting that it comes under the aegis of public health.

In defining their interest in safety for this blood program, the Provinces and Territories through their Agency must consider the following factors:

1. That the Federal Government through the BoB has the primary regulatory role in safety and that the role of the Agency is to provide support and advice for this role.
2. That the Agency has a role in safety because of the interest and concerns of the Provinces/Territories in safety because it finances the program and therefore must evaluate the cost of providing progressively higher levels of safety particularly:
 - when no standard has been established
 - when two or more courses of action meet a standard
 - when the Bureau merely recommends a standard but does not make the standard mandatory.
3. That the CRCS has the primary operational role in the system and that the role of the Agency is to respect the Society's first obligation to comply with BoB standards. The Agency must also seriously consider the CRCS requests for funding to improve safety when there is no standard, when there are operational options for meeting a standard or when a standard is simply recommended by BoB.

3.2 Regulation

The National Health and Welfare Act gives the Minister of Health broad powers concerning the promotion and preservation of health in Canada. Among the statutes the Minister has responsibility for is the Food and Drugs Act. This defines drugs, sets out a regime for inspection and enforcement and provides authority for the development of regulations. Blood and blood products are regulated as drugs under

the Act. Division 8 of the drug regulations (Part C) applies to all drugs, and Division 4 is specific for biologic drugs. Manufactured blood products such as factor VIII and factor IX have been regulated since their commercial production began (the first licence was issued in 1968). Collection of plasma by plasmapheresis was added to Schedule D of the Act in 1978 and blood in 1989. The Act and regulations are administered by the Drugs Directorate of the Health Protection Branch of Health Canada. Within the Drugs Directorate, the Bureau of Biologics is responsible for regulation of biological drugs, which include blood and blood derivatives.

3.2.1 Bureau of Biologics

Within the Bureau of Biologics there are a number of divisions. Those directly involved in the regulation of blood and blood products are the Compliance Division and the Blood Products Division. The latter consists of several sections: Coagulation, AIDS Vaccine/Plasma Derivatives, Blood Bank and Biotechnology.

In Canada, both biological products and the facility making them have to be approved. The data submitted in support of a new drug are regulated under Division 8 of the regulations, and the facility is regulated under Division 4. As biological products are so much more complex than other pharmaceuticals and there is a greater degree of variation in starting materials, emphasis is put on the suitability of the manufacturing facilities, the manufacturing procedures and the quality control testing.

There are four stages in licensing a biologic drug: review of the manufacturing process, inspection of the facilities, review of clinical data and independent testing. For blood and blood components, only the first two are significant, but for plasma derivatives and products to replace plasma derivatives, all four stages are important.

a) Blood and blood components

There are no regulations specific to blood and blood products. When blood was added to Schedule D in 1989, the Regulatory Impact Statement published in the *Canada Gazette* (Part II, Vol 123, No. 8) stated:

Therefore Schedule D drugs may not be sold until premises of the manufacturer are inspected to demonstrate that manufacture and testing produce a drug product of quality. Facilities of these manufacturers are inspected annually and are licensed by the Department ... This licence indicates that the premises in which a drug was in whole or in part manufactured, and the process and conditions of manufacture are suitable to minimize the risks associated with these drugs.

A set of guidelines for Blood Collection and Blood Component Manufacturing was issued in 1992. These guidelines provide reference standards and define minimum criteria for facilities in Canada. It is stated that the principles and practices described are acceptable to the Health Protection Branch and following them should ensure compliance with the appropriate standards and regulations. They do not apply to blood components collected by a hospital for use within the hospital or procedures performed by a hospital. The guidelines contain guidance on: collection and testing, storage and preparation of whole blood and blood components, apheresis, and quality assurance and labelling. An important aspect of each section is the requirement for Standard Operating Procedures.

A detailed Standard Operating Procedures (SOPs) manual must be made available to the personnel at each blood centre. A procedure must be in place for review and approval of SOPs. The SOPs must be reviewed and updated whenever processes are significantly revised or changed. All revisions must be documented.

With respect to the design and construction of facilities, there is a requirement to include features that prevent hazards that might adversely affect the quality of the product. Reference is made to Good Manufacturing Practices in Section C, Division 2, of the drug regulations. Although the GMPs do not legally apply to drugs listed on Schedule C and D, they are taken as guides. GMPs are being developed for biological drugs.

A set of guidelines called Inspection of Biologics Manufacturers was also issued in 1992. This document describes what biologics manufacturers can expect to occur during a plant inspection and identifies some of the information that an inspector may request for review.

The Compliance Division is responsible for developing policies, coordinating premarket approval, organizing Canadian and foreign inspection programs to ensure that manufacturers comply with acceptable manufacturing standards and being the designated contact for public inquiries and liaison with manufacturers. This division is also responsible for issuing Canadian biologics licences, which need to be renewed annually.

b) Plasma derivatives

Plasma derivatives and plasmapheresis have been covered by the Act for a longer period of time than has blood. There are specific regulations in Section C, Division 4, dealing with human plasma collection. When derivatives are new or variations of old derivatives (eg albumin), New Drug Submissions and/or Investigational New Drug Submissions are required as part of the licence application. Guidelines for these filings were published in 1991. The publications state that the guidelines are not

intended to be exhaustive or inflexible, but that they should ensure compliance with the regulations. Deviations may be judged acceptable following discussion with the division of the reviewing bureau. Early consultation with the bureau is encouraged.

There are also guidelines for plasma derivatives that are manufactured by other means, eg, recombinant technology. These applications are reviewed within the biotechnology section of the Blood Products Division of the Bureau of Biologics.

An application is first examined by the Compliance Division to determine whether it is complete and acceptable for review. Forty-five days are allowed for this. Then there is a possible shelf time of 150 days (unless there is a request for fast-tracking). The time allowed for review is 270 days. The review involves a detailed examination of the manufacturing procedures in the submission as well as the quality control testing. Three to five consecutive lots (depending on the product) are required and tested at the laboratory of the Bureau of Biologics (this requirement is unique to the review of a biological submission). The clinical data are also reviewed and the facility inspected. When all of these are completed and considered adequate, a biologics licence may be issued, along with a notice of compliance and drug identification number for the product. But as drugs on Schedule D are released on a lot-by-lot basis, the manufacturer is required to submit samples for each lot to be sold in Canada, along with quality control protocols for evaluation, testing and lot release.

Of particular significance to safety are the potential for contamination with infectious agents or foreign proteins (this is assessed by reviewing the manufacturing process), and adverse drug reaction analysis (this is assessed by reviewing the clinical data). The types of information sought and used in the analysis include: frequencies of local and systematic reaction, life-threatening events and their relationship to dose and reversibility, as well as whether there is any correlation with important subgroups of the population. These are considered in the context of the frequency and severity of the disease and other characteristics of the target population.

3.2.2 Bureau of Medical Devices

Medical Devices Regulations under the Food and Drugs Act, regulate the safety and effectiveness of *in vitro* diagnostic kits, including those for HIV. There is a plan to have the kits, which are used for screening blood, added to Schedule D of the Act and to regulate them as drugs. This change would introduce lot-release procedures and specific inspection and licensing of manufacturing facilities as elements of the regulatory process. At present, the kits regulated under the Medical Devices Regulations fall into two groups: those that require notification **after** the product enters the market and those listed in Part V of the regulations that require a notice of

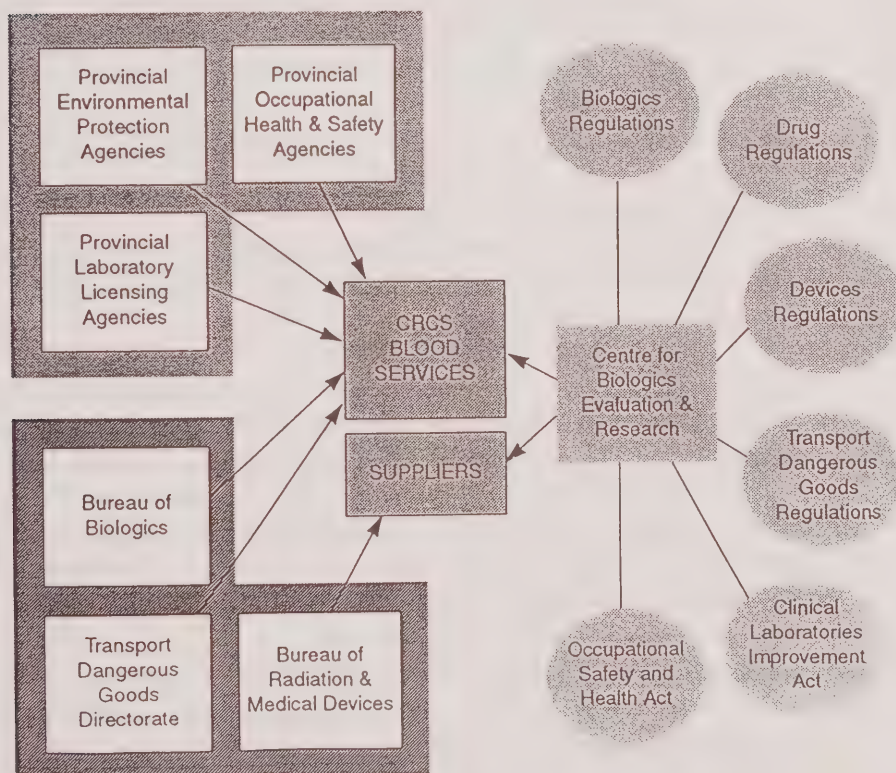
compliance **before** the device enters the market. In 1985 the regulations were amended to move HIV test kits into Part V. These regulations are administered by the Bureau of Medical Devices.

Although the Bureau of Biologics is not involved in the approval of the kits at present, it assesses the adequacy of the kits used to identify donations carrying infectious disease markers. This assessment is part of the review of the manufacturing process required before blood collection centres or plasmapheresis operations are licensed.

3.2.3 Other statutes and regulations

There are a number of other statutes and regulations that directly or indirectly deal with the safety of blood and blood derivatives. Among these are statutes in some provinces governing the operation of laboratories. Most of the other regulations that have an impact on the system deal more with health and safety of the public, workers and the environment (see Figure 3).

FIGURE 3
Regulatory environment



3.3 Blood supply subsystem

The blood supply subsystem in Canada is, almost exclusively, in the jurisdiction of the Canadian Red Cross Society.

The stated role of the Blood Services Program of the CRCS is to provide Canadians with a safe and secure supply of blood using a wholly integrated service, from donor recruitment to distribution of blood components and fractionation products to health care institutions.

3.3.1 Canadian Red Cross Society

The CRCS was originally incorporated by a special act of Parliament in 1909. The Society was given status in 1970 as a federally chartered private not-for-profit corporation. From the end of World War II until 1973, it supported a free blood program funded primarily from its own charitable receipts. Since 1973 the Blood Services Program has been funded almost exclusively by the provincial and territorial governments.

The National Director of Blood Services, along with national directors for field services, international services and human resources, reports through the secretary-general to the Board of Governors.

The national blood service consists of:

- (a) Blood Services at National Office
- (b) National Testing Laboratory at National Office
- (c) Seventeen regional blood centres across Canada
- (d) Blood donor recruitment network, which has recently been amalgamated with the regional centre operations.

The direct overview of the Blood Services Program is the responsibility of the National Blood Services Committee, which reports to the Board of Governors. The Board is responsible for all major policy decisions affecting the Blood Services Program. In making its decisions the Board receives advice from the National Blood Services Committee. The structure and function of this committee is currently under review and explained in detail in a response from the CRCS to Recommendation 8 of the Deputy Ministers' Task Force on Blood Issues.³

At the discretion of the National Director and senior staff, working groups can be formed to assess issues that may affect the safe and efficient operations of blood services. Recommendations from the working groups are presented to the National Director and senior staff group for their consideration. Recommendations that are

approved are put forward to the National Blood Services Committee, which documents its reasons for implementation or rejection of the recommendations.

At present there are three standing working groups: labelling practices, donor selection criteria, and blood components. The membership may include personnel from CRCS National Office, from regional centres and from outside the CRCS, such as hospitals.

The Red Cross operates the only blood service in Canada. As a de facto monopoly, the Red Cross has responsibility for maintaining not only the safety but also the security of the nation's entire blood supply. The Red Cross defines its corporate mandate as follows:

- to manage blood service operations effectively
- to ensure that the processes and products meet all regulatory and industry standards
- to plan and prepare for the future product requirements of Canadian institutions
- to support research in blood transfusion medicine.

National Office

The National Director oversees the operation of Blood Services and is designated the "responsible head" for purposes of licensing and regulatory supervision. As Blood Services is a national program, administered through the 17 regional centres, the direction, policies and most of the planning and design of the operations take place at the National Office.

In 1992 Blood Services went through a major restructuring at the National Office. The goal was to improve the efficiency, responsiveness and cost-effectiveness of services and product delivery. There are four departments covering administrative and operational issues: management services, quality and standards, regulatory affairs, and manufacturing and development.

The management services department has responsibility for budgeting and financial analysis, computer services and materials management.

The budgeting and financial analysis section of the department is responsible for preparing the blood program budget, liaison with CBA and provision of information on matters that have funding implications. This section also has developed a standardized reporting format, which includes production data. Reports are prepared that include variance analysis and investigation, forecasts and balance and income statement sheets.

The computer services section is responsible for the computerized financial system as well as maintenance and support for computer systems at the regional centres. At present the main system is Blood Information System (BLIS), which was introduced in 1981 as a donor recruitment tool. It has been enhanced repeatedly over the years to gather complex data required by donor screening and testing. It is recognized, however, that the hardware and software have many limitations. There are 22 computer-based information systems at national and regional levels in various stages of development, upgrade or general maintenance. The Computerized Information Systems for Centre Operations (CISCO), the most ambitious information system project to date, was started in 1989. The pilot project is based in the Edmonton blood centre, with implementation planned for other centres in 1995.

The materials management services section negotiates contracts for major purchases, such as blood packs, test kits, vacutainers and other medical supplies used at regional centres. At this time, there are no national contracts for major equipment used by the centres. Personnel meet with manufacturers to discuss any current problems and a technical committee meets with a specific manufacturer (Miles) to discuss evolving new technologies.

The quality and standards department works with staff from the regional centres. It has recently produced an entirely new set of Standard Operating Procedures. These are being submitted to the Bureau of Biologics and are being pilot-tested in three regional centres. The department provides support for the centres. They analyse quality control data from centres and monitor product defects and results from the College of American Pathologists proficiency program. A specific example of the work of this department is the computerized (bar-coded) confidential unit exclusion program for use in all centres, which will be piloted and implemented along with the new SOPs.

The regulatory affairs department is responsible for the approval of all SOPs, centre audits, adverse reaction reports, lookback and traceback reports, corrective actions and for all communications with BoB. Centre quality assurance specialists collaborate with this department to ensure regulatory compliance of centre activities.

The manufacturing and development department has four sections: plasma fractionation products, HLA laboratory, serology laboratory and a development unit. The fractionation section is responsible for the distribution, through the blood centres, of the CRCS's plasma fractionation products. The HLA section produces HLA serological trays for use in centres and hospitals fulfilling 80% of Canada's need. It also does molecular HLA typing for the Unrelated Bone Marrow Donor Registry. The serology section produces serological reagents for red cell typing and serves as a

reference lab for phenotyping and rare antibody investigations. The development unit tracks developments that could affect centre activity.

From this summary, it is clear that the National Office of the CRCS holds most of the major responsibilities for priorities, direction, funding, planning, program design, regulation and licences for the Canadian blood supply subsystem.

National Testing Laboratory

The National Testing Lab (NTL) is responsible for evaluating new test kits, validating test kit software, writing SOPs for all tests, communicating on problem issues with test kit manufacturers and lot-releasing all kits for regional centre use. It also performs site inspections of all test kit manufacturers, not only to assure compliance with cGMPs, but also to assess the capacity of these manufacturers to supply all of Canada. NTL is also involved in evaluating and qualifying equipment, such as the Olympus blood grouping machine, and implementing syphilis and cytomegalovirus (CMV) tests on this equipment. At this time, NTL is evaluating a new model Olympus and is coordinating the writing of test script for validation purposes. The laboratory is also involved in developmental research on HIV and hepatitis C virus (HCV) testing along with basic research.

Reference serology work has become a small part of the operation as expertise within the centres has developed. However NTL is still actively involved in bulk purchase of typing reagents, which are bottled for distribution to the centres. Other functions of the NTL include confirmatory testing for HIV, hepatitis B surface antigen (HBsAg), human T-cell lymphotropic virus (HTLV) and HCV, as well as total protein measurement for plasmapheresis donors.

Regional blood centres

There are 17 regional blood centres across Canada. All except the centre in Charlottetown, Prince Edward Island (which is supported by Halifax regional centre), are responsible for their own recruitment, collection, processing, testing and distribution of blood and blood products. Each centre is headed by a medical director, who reports directly to the National Director at the National Office.

The core services of every blood centre include: recruitment, collection, processing, storage and distribution of blood components and fractionation products, as well as clinical consultation on the use of these products.

The following products and services are provided by the centres:

- red cell concentrate (packed red cells)
- leukodepleted red cells
- washed red cells
- frozen washed red cells for rare phenotypes and antibody problems
- autologous collection
- red cell phenotyping and antibody investigation
- random donor platelets
- single donor platelets (HLA matched or otherwise)
- CMV-tested blood components
- fresh-frozen plasma
- cryoprecipitate
- plasmapheresis plasma for fractionation
- teaching for medical residents and lab technologists.

Depending on local needs, centres also provide other services such as cross matching, prenatal testing, HLA typing, peripheral blood stem cell collection and storage, marrow separation and cryopreservation, total plasma exchange and operation of the Unrelated Bone Marrow Donor Registry.

In provinces such as British Columbia, Alberta and Manitoba, which have extensive remote northern communities, the Red Cross does regular infectious disease testing of individuals who may be used as emergency blood donors by local hospitals.

The centres also distribute a number of plasma derivatives and other products to hospitals including: albumin, factor VII, factor VIII, porcine factor VIII, factor IX, high-purity factor IX, feiba, immune globulin, Rh immune globulin, hepatitis immune globulin, Varicella-Zoster immune globulin, intravenous immune globulin, and CMV intravenous immune globulin. Some of these are derived from Canadian plasma that is shipped to the United States for fractionation; others are purchased from commercial sources.

3.4 Process

Operations performed at the regional blood centres include the following.

- 1) Blood donors are recruited.
- 2) Donors are registered.
- 3) Donors are screened by health assessment questionnaire, interviewed by a nurse and given a confidential exclusion option. Their blood is tested for specific gravity (surrogate for hemoglobin measurement) and or hematocrits, and ABO type for new donors.

- 4) If, at the end of the screening, the donor is assessed fit to donate blood, his or her identity is checked, there is a visual check for needle marks, the arm is disinfected and venipuncture is performed.
 - 5) Blood is collected: 450 ml of whole blood is collected into a prepared blood pack that contains anticoagulant. During collection the donors are monitored, and the packs are rocked (for mixing with anticoagulant). Volume is estimated by weight. Labelling occurs at this time as does the collection of laboratory samples.
 - 6) Blood packs are sent for preparation and the samples sent to the lab for testing.
 - 7) Blood components are prepared, by either centrifugation or gravity sedimentation. Depending on need, various components are separated. Storage depends on the particular component. Included among the components are: red blood cells, which may also be washed, leukocyte-reduced or frozen (glycerolized); plasma, which may also be fresh frozen, frozen, platelet-rich or cryoprecipitated antihemophilic factor (AHF); platelets and occasionally granulocytes.
 - 8) Samples of the donors' blood are tested for
 - ABO group determination
 - Rh type (using anti-D, if negative then tested for weak D)
 - unexpected (clinically significant) red cell antibodies
 - transmissible disease markers: anti HIV-1 and 2, HBsAg, anti-HCV, anti-HTLV I/II, syphilis, and anti-CMV (as needed).
- These tests are automated with a varying degree of software for recording results.
- 9) Results are collated and then components are sorted and labelled.
 - 10) Those components that are unacceptable, because of the results of the tests, or for other reasons, such as damaged packs, are labelled "not for transfusion", and are quarantined and destroyed.
 - 11) Components deemed for transfusion are sorted and stored.
 - 12) Requests from hospitals or users are received and filled,
 - 13) Products are transported.

There is considerable documentation at each step, both in terms of standard operating procedures, indicating what should be done and the criteria, as well as records of what is being done with each unit. Many double checks are built into the system to ensure that the components are labelled correctly, test results are linked to the correct components, and that all steps are documented so that units and records can be traced. The lot or batch numbers of the packs used, the reagents for testing, time and temperature of testing and production, dates and temperature of storage, and names of personnel performing and overseeing the processes are all documented.

Quality assurance is required at each of the centres. The quality assurance officer is responsible for ensuring that policies and procedures are properly maintained and

executed and that reagents, equipment and methods function as expected. The program involves:

- standard operating procedures for all operations
- proficiency testing
- review of errors and adverse effects
- review of records to ensure completeness, accuracy and adequacy (sign offs and dates)
- review of quality control testing
- ensuring equipment is maintained and calibrated, and tests validated
- training and ensuring that training records are maintained.

The basic operations involved in the process of collection, processing and testing of blood have become increasingly complex. Whole blood is no longer the only product and the number of tests has increased, especially for transmissible diseases (Table 4). As the number and complexity of steps in the process increase, so do the expectations of the public and regulators. This expectation has led to a change in philosophy from that of a health care service to that of a drug manufacturer. There is a greater emphasis on process controls, quality assurance and total quality management.

Table 4
Tests performed 1984-1994

SCREENING TEST	84	85	86	87	88	89	90	91	92	93	94
Syphilis	X	X	X	X	X	X	X	X	X	X	X
HBsAg	X	X	X	X	X	X	X	X	X	X	X
Anti-HIV I		X	X	X	X	X	X	X			
Anti-HTLV I							X	X	X	X	X
Anti-HCV							X	X			
Anti-HIV 1/2									X	X	X
Anti-HCV 2.0									X	X	X

Donor selection criteria

National guidelines have been established to assist nurses and physicians at blood centres to assess an individual's eligibility to donate whole blood or other blood components. These donor criteria are reviewed periodically and approved by the Bureau of Biologics. The principles are: 1) that the donor should suffer no harm by donating and 2) that the donor does not suffer from any illness that could be

transmitted to a recipient by blood transfusion. Currently a healthy individual between 17 and 70 years of age may donate up to five times a year. The identity of the donor must be established. Careful screening of donors by clinic personnel takes place before each donation. Donors also have to complete a confidential self-designation form to say whether or not their blood is fit for transfusion.

3.5 Research

Many of the scientific and medical staff in the centres carry out research in transfusion medicine and related disciplines. Their activities are supported both by intramural grants and funds from outside agencies. The Red Cross's intramural research and development (R&D) program is funded by the CBA. There are research grants for work in basic disciplines such as molecular biology, immunogenetics and gene expression, as well as transfusion medicine.

Supported by funding from the CBA and Miles Canada Inc. through the CRCS, a scholar program has been established. Another joint program between the CRCS and Miles funds R&D efforts relevant to transfusion medicine, the safety and efficacy of blood and blood products and the delivery of transfusion-related services. These grants are not restricted to the CRCS.

In order to attract physicians to the specialty of transfusion medicine, the CRCS offers one or two years of training in the specialty at the various blood centres.

Extramural R&D grants are available to scientists and physicians both inside and outside the CRCS. Such funding agencies include: Medical Research Council, the National Health Research and Development Program of Health Canada, the Ontario Ministry of Health, the National Cancer Institute and Supply Services Canada. Details of the projects and the workers within, or affiliated with, the CRCS can be found in the *Statistical Report: Blood Services*, published annually by the Red Cross.

Blood Services Program has also established a Career Development Fellowship Award Program for highly qualified physicians and scientists to gain further experience in blood centre environments.

3.6 Statistics

Table 5 is a brief summary of the number of units collected and transfused and components prepared.

Table 5
Summary of blood service activities

	1993-1994	1992-1993	1991-1992
Donors attended whole blood clinics	1,129,817	1,195,676	1,286,613
Donors deferred	84,068 (7.4%)	100,998 (8.4%)	115,432 (9.0%)
Whole blood units collected	1,045,749	1,094,679	1,171,181
Plasmapheresis units collected	116,048	110,728	108,192
Platelet apheresis units collected	6,432	7,602	
Granulocyte apheresis units collected/transfused		128/44	73/51
Stem cells	242	48	
Red cell units transfused		867,739	944,903
Platelets prepared		514,825	534,123
Cryoprecipitated AHF prepared		93,727	92,869
Factor VIII units issued		79,425,705	67,596,170
IGIV grams issued		632,366	473,129
Autologous collections	13,433	9,624	6,519

Source: Statistical Report of the Canadian Red Cross Society

4.1 Introduction

Safety is generally considered to be the absence of risk. Safety is assessed by identifying and estimating, as accurately as possible, the level of risk. For the blood system this is done by assessing risks at the various steps: selection of blood donors, processing and testing of the donated blood, and use of the blood or blood products. It must be recognized that, even with optimal, state-of-the-art methods for risk reduction, the use of blood and blood products will never achieve absolute safety. Therefore, in making decisions regarding the use of blood or blood products, it must be clear that the benefits outweigh any residual risk.

This part of the report begins with a brief description of public perception of risk and the use of blood and blood products in relation to the need or benefits derived from them. A short description of the measures of risk follows, as well as the sources of data that can be used to estimate risk and the limitations of the data. This is followed by a summary of factors within the system that influence or cause risks. Finally, a description of the known risks from the use of blood products in health care, including available estimates of frequency and outcome is provided.

4.2 Public perception of risk

When assessing the current safety of the Canadian blood supply, the perception of risks by both experts and the public assumes importance. Scientists skilled in risk management and the public do not necessarily perceive risk in the same way.⁴ In one study, experts and members of the public were each asked to rank 30 activities according to level of risk. The public placed nuclear energy as the riskiest activity, whereas experts placed it 20th.⁵ Similarly, the public continues to believe transfusions are unsafe. Recently it was reported that a survey found that 25% of Canadians would not accept a blood transfusion.⁶

It is clear that public policy about risk acceptance must include an analysis of public perception.⁷ Blood transfusion risks are seen to be largely involuntary and, as such, are accepted poorly by the public when compared to voluntary risks such as mountain climbing.⁸ The public will accept risks from voluntary activities that are roughly 100 times greater than those posed by involuntary activities, given the same degree of benefit.⁹ Generally, it is poorly understood that eliminating or reducing one risk may increase other risks. For example, reducing the risk that a transfusion recipient will

succumb from a transfusion-transmitted disease may increase the likelihood that the same recipient will die from cancer.¹⁰

Models of acceptable risks have been developed in other areas of medicine, especially in dealing with ionizing radiation.¹¹ For example, views of the permissible levels of radiation developed over several decades and the concept of "as low as reasonably achievable" (ALARA) emerged.¹² A similar concept has been proposed that could be introduced to define acceptable transfusion risks.¹³

The improvement in safety of the blood supply by implementing a preventive strategy can be estimated as it has been for HIV-1 antigen testing.¹⁴ These estimates should be widely shared with the public. However, it is unlikely that the public will find such risk assessments and decisions about risk reduction acceptable unless all feasible protective measures against AIDS transmission are instituted.

4.3 Benefits

The benefits of transfusion are measured not only by lives saved, but also by the decrease in morbidity and increased support provided for medical and surgical procedures. The management of many diseases such as coagulation disorders depends on blood products. Many current medical and surgical interventions, such as open-heart surgery, solid organ transplantation, bone marrow and stem cell transplantation, and extensive resection of malignant tumours, would not be attempted if blood transfusions were not available. Two-thirds of red cell transfusions are in support of elective surgery and resuscitation in cases of severe trauma.¹⁵

4.4 Measures of Risk

Risk is the chance of an incident occurring. Unfortunately, most measures of risk are based on past experience. In interpreting these estimates, one must take account of the effects of changes that have occurred since.¹⁶ Furthermore, few data exist about current transfusion risks in North America, and even fewer data exist in Canada. This is due partly to the passive reporting of both adverse reactions and infectious disease transmission.

The accuracy of measurements of risk depends on the adequacy of the systems in place to collect and analyse data. As will be described below, there are serious limitations to the data currently available. Generally, for infectious diseases, prevalence data are available; therefore estimates of risk can be made using these data (with certain assumptions), rather than having to rely solely on data on transfusion-

transmitted infections. Where data are less complete or reliable, precise estimates are not possible and risks are described in qualitative terms.

In order to understand measures of risk for infectious disease, it is important to define some of the terms being used.

Prevalence is the proportion of a population with a given condition. When estimating prevalence, it is irrelevant whether the condition is newly acquired or long-standing. This report will refer to the prevalence of positive tests for a condition like HIV-1 or HCV among a group of donors or among a group of donations.

Incidence is the rate at which a condition is being newly acquired in a population during a period of time. In the context of repeat donors, annual incidence rates are usually calculated as the number of new cases divided by the number of person-years of observation during which these conditions were acquired.

Newly acquired cases are sometimes referred to as **incident** cases, whereas cases of longer duration are called **prevalent** cases.

When estimating the risks for transmission of an infectious disease, it has been assumed that one group of donors is less safe than a second group if they have a higher prevalence of a positive test for that agent. This is based mainly on experience with paid donors in the United States in the early 1970s, and the high prevalence of hepatitis B in this population. The rate of positive tests for hepatitis B in the paid donors was several times higher than that in volunteer, unpaid donors. When remuneration for donors of whole blood was virtually eliminated, hepatitis B transmission by transfusion decreased dramatically. The assumption that positive test rate is related to risk underlies many of the estimates that follow.

4.5 Sources of data for estimating risk and their limitations

Data on adverse reactions experienced by recipients are important for assessing the safety of the blood supply. In guidelines developed by the Bureau of Biologics, *Blood Collection and Blood Component Manufacturing Part IV: Quality Assurance and Labelling*, a section on review of adverse effects and transfusion complications states:

A system for documenting and evaluating suspected transfusion complications must be maintained. All reported transfusion reactions must be promptly investigated to the extent considered appropriate by the blood centre's licensed physician.

Fatalities resulting directly from transfusion or from donor collection must be reported to the Bureau of Biologics within one working day of the event.

At present the means of tracking this information include:

- Hospital records. Recording adverse reactions is the responsibility of the treating physician and, if serious, they should be reported to the regional blood centre. The National Office of the CRCS has a record and follow-up information on all the reactions reported to the centres. This has been required only since March 1992. Of the 30 or so reactions reported in the past year and a half, many, including several fatalities, are unresolved or unresolvable with respect to cause. The most severe reactions are also reportable to the Bureau of Biologics.
- Reports the CRCS submits to the Bureau of Biologics.
- Transfusion-related deaths registered on death certificates.

However, at this time, there are serious limitations to the use of these data for estimating the risk of adverse reactions to the use of blood or blood products. These include:

- a) Identification of adverse reactions has to begin with treating physicians. In many cases, recipients have serious and complicated (often fatal) conditions that can obscure adverse reactions to a transfusion. The recipients may not live long enough for adverse events (such as an infectious disease) to be manifested. The recognition that the reaction is associated with the transfusion (or treatment with a blood product) can also be very difficult as recipients may have had other exposures to put them at risk or may have concurrent complex illnesses.
- b) The means of recording or analysing outcome data are not uniform or universal.
- c) For infectious diseases transmission, identification and tracing are somewhat easier and units can sometimes be traced back to donors. In some cases it may be possible to determine the status of the donor at the time of donation in order to ascertain whether the donation was reactive (therefore an error had allowed it to enter the system), or whether a subsequent donation from the same donor was reactive (indicating that the donor may have been in the window period and seroconverting at the time of the donation in question). However, in many cases, although the identity of the donor can be established, follow-up is difficult. Also it is unknown whether the recipient had exposure to other sources of infection.
- d) Since the latency period for infections is variable, there can be a lag in recognizing transfusion-transmitted infections and data indicating trends cannot be considered complete until 10 to 15 years after transfusion or treatment.
- e) Indefinite record retention for traceback purposes has been required only within the last 10 years.
- f) Data collected from death certificates listing transfusion reaction as a cause of death are very inaccurate.

For these reasons, the safety of the blood supply cannot be measured accurately by the number of failures. Instead, one must assess the effectiveness of measures to control

safety. For instance, for most of the known transmissible diseases, tests are available to identify whether or not a donor is infected.

The National Testing Laboratory of the CRCS does confirmatory testing on samples that are repeat reactive for transmissible disease markers. Statistics are collected on the number of repeat reactive samples, confirmed positive and indeterminate results for all transmissible disease markers. These data are useful for estimating prevalence in the donor population and for identifying trends. The limitations on the use of these data for assessing safety and projecting trends include:

- a) Most data from NTL are per donation. This means that the higher rate of repeat reactive samples among new donors compared with samples from repeat donations can be partly explained by the fact that some repeat donors may donate several times a year.
- b) Repeat reactive samples have, since 1992, caused the donor to be permanently deferred, even if confirmatory tests are negative. As will be discussed later, the impact and significance of this policy increases as the number of false positive test results increases, ie, specificity of the test decreases. Decreases in the specificity of a test often occur when the sensitivity is increased.

Other types of data that can be useful for estimating infectious disease risk are prevalence and incidence rates in the general population (potential donors). Public health authorities are responsible for disease surveillance at the local level. Some diseases are reportable, which means the data are collected and ultimately submitted to the Laboratory Centre for Disease Control. However, in most cases, disease reporting is passive and varies from one region and province to another within Canada.

International data on surveillance and disease incidence and prevalence are available through a variety of sources, notably the World Health Organization. Although international data and trends are reviewed by a variety of groups within Canada, they are not the clear mandate of any one group. Because cultural, genetic and geographic differences have a profound effect on the presence and spread of disease, international data cannot be relied upon for predicting trends and estimating risk in Canada. One other limitation of using these methods for predicting or anticipating risks is that, generally, we can detect only what we look for.

4.6 Sources of risk

4.6.1 Blood supply subsystem errors influencing risk

Blood centres, which are the facilities that manufacture blood components for patients in Canada, are extremely complex. (See blood centre diagram in Appendix X.) Because of this complexity, process controls in the blood centres are exceedingly

important. Every box in Appendix X represents multiple tasks, and a lapse during the performance of any task can increase risks to transfused patients. Good manufacturing practices provide guidance for reducing risks through the use of process controls.

Processing errors or deficiencies in the blood supply subsystem can lead to a variety of types of risks. For example:

- 1) The release of an infectious unit of blood can result from: failure of the detection system (false negative test result) or errors in transcribing results of laboratory tests
- 2) Blood or blood products could be contaminated because of ineffective arm preparation, contaminated or faulty bags or equipment, or lack of aseptic technique during component preparation.
- 3) Immunologic reactions in recipients due to improperly matched cells can result from transcription errors or mislabelling.
- 4) Other adverse reactions in recipients can result from low-quality products or products that are contaminated with other components or cell metabolites (for example, cytokines from lymphocytes). Low-quality products can be released because of inadequate quality control, and errors in calibration and validation of process, equipment and temperature control for storage and separation.

4.6.2 Clerical error by health care providers

Clerical and management errors in hospitals remain among the leading causes for the transfusion of incompatible red cells. Between 37 and 54 percent of such misadventures, some of which result in death, are due to these causes.¹⁷ Limited computerization, particularly absence of links between blood centres and hospital transfusion services, may marginally add to this risk in Canada.

4.6.3 Other systems failures

Less obvious sources of risk reside in manufacturing failures outside the blood supply subsystem. Among these are errors in manufacturing reagents, supplies, and equipment, including computers, used by blood centres in testing and manufacturing blood components. The reduction of these risks is the objective of regulating blood centre suppliers and vendors.

4.7 Types of risk from blood transfusion in 1994

4.7.1 Transmissible disease risks

A unit of blood carrying the agent of a transmissible disease could be released by the supplier through one of three mechanisms. First, the donor may have only recently been infected with the agent (an incident case) and the elapsed time may have been too brief for a blood sample to react in the test. In the case of HIV-1, for example, there is a period after infection during which the antibody concentration in the blood has not yet risen to detectable levels. In the case of hepatitis B, there is a short period after infection before the surface antigen is detectable. This interval is commonly referred to as the "window period" and its length depends on the particular infection and the technology that is used in the test. It is the incidence rate among donors together with the duration of the window period that primarily determine the risk that a positive unit of this type will be released. For convenience, we refer to this as a group I error.

The second mechanism occurs due to failure of the test to detect units of blood donated by individuals with established infection (prelatent cases). Such incidents are termed "false negatives" and occur whenever a test has less than 100% sensitivity. The risk that a positive unit will be released in this way is determined primarily by the prevalence rate of the infection among donations and the false negative rate. We term these group II errors.

The third mechanism occurs due to failure to remove units of infectious blood because of system errors. Such system failures might happen due to transcription error or mislabelling, which results in a positive unit remaining in the supply. The risk that a positive unit will be released by this mechanism is determined primarily by the prevalence rate of infection among donations and the system error rate. We call these group III errors.

Human immunodeficiency viruses 1 and 2

HIV-1 and HIV-2 are retroviruses, both of which cause AIDS. However, in most parts of the world, HIV-1 is by far the more common. Screening for both viruses is done simultaneously on all donated blood. It is not known whether all persons infected with HIV will eventually go on to develop AIDS and die. Within 10 years of infection, approximately 50% of individuals will have developed AIDS¹⁸ and there is evidence that this percentage continues to increase with time after infection. Despite advances in therapy, AIDS remains a fatal condition.

In order to estimate infectivity rates, Monte Carlo simulations of HIV-1 in the Canadian blood supply were conducted. These are described more fully in Appendix VII. Simulations relied upon empirical data from the scientific literature and from Canadian sources whenever possible. It was concluded that, using reasonable assumptions, approximately one to four HIV-infected donations will likely escape detection in Canada in 1995. The likelihood is greater than 90% that the number of infected donations escaping detection will be within the range of one to four. This corresponds to a risk of 1 in 750,000 to 1 in 188,000 per donation. Given that each donation can give rise to three components (red cells, plasma and platelets), the number of different people receiving infected components would be in the range of 1 to a theoretical maximum of 12.

The risk of HIV transmission due to group I errors is far greater than the risk due to group II or group III errors. Insensitivity in the test system to detect prevalent cases of HIV-1 infection among blood donors contributes little to the risk of HIV-1 transmission compared with infectious blood units from donors in the window period. While methods for direct viral detection (eg polymerase chain reaction (PCR) technology, antigen capture, etc) may decrease the time during which the donor can escape detection, there may be other less costly types of activities that can prevent potentially infected donors from entering the system. These include more stringent methods of donor screening. Intensive screening of first-time donors may lower the relative risk (see 5.6 Donor recruitment, screening and retention). This is underscored by the fact that although first-time donations represented only 11% of all donations in Canada in 1993-94, they represented almost half (10 of 23) of all prevalent cases of HIV-1 infection among donations.

With regard to HIV-2, the current screening process detects prevalent cases. Given that only a handful of cases of HIV-2 have been detected to date in Canada, it is estimated that the risk of transmission of HIV-2 due to group I error is extremely low.

Human T-cell lymphotropic viruses I and II

The human T-cell lymphotropic viruses, type I (HTLV-I) and type II (HTLV-II), were the first human retroviruses to be discovered. They belong to a subclass of retroviruses distantly related to HIV. As with HIV, the presence of antibodies is taken to mean that the individual is infected with the virus.

Two diseases have been associated with HTLV-I: adult T-cell leukemia/lymphoma (ATL) and a chronic degenerative neurologic disease called HTLV-I associated myelopathy or tropical spastic paraparesis (HAM/TSP). ATL, which occurs many years after infection, is estimated to develop in 2 to 4% of persons infected with HTLV-I at an early age and takes at least 20 to 40 years to develop¹⁹. HAM/TSP has

a shorter latency period and is less common than ATL, occurring in less than 1% of infected individuals.

HTLV-II is less prevalent in Canada than HTLV-I, but relatively more common in users of injected drugs. Association with disease has not clearly been established although a recent study suggests an increased incidence of neurologic disease.²⁰

All blood donations in Canada are screened for HTLV-I and II by a single test, which does not distinguish between the two. The prevalence of antibodies to HTLV in blood donations in Canada in 1993 was 3.2 per 100,000.²¹ In a donation base of 1,900,000 units in 1991-2 in the U.S., the annual incidence of HTLV seroconversion was 3 per 100,000.²² The window period for HTLV is poorly defined, which makes precise estimates of risk difficult. If the incidence in Canadian donations is even lower, this suggests that transfusion of units taken during the window period that lead to overt disease will be extremely rare, even if the window period is wide.

Hepatitis C virus

Hepatitis C virus (HCV) is a major cause of acute and chronic hepatitis. The majority of people who become infected with HCV will remain chronically infected and at least 50% will develop chronic hepatitis. This will lead to cirrhosis in at least 20% of those with chronic hepatitis and to liver failure in 5%. These complications take 15 to 20 years to develop. The progression of post-transfusion hepatitis C to hepatocellular carcinoma in a small number of cases is well documented and also takes many years to develop.²³

The introduction of screening tests for antibodies to HCV has significantly reduced the risk of post-transfusion hepatitis.²⁴ For example, in the Canadian blood system in 1993, a total of 648 blood donations were found through recombinant immunoblot assay to have antibodies for HCV and were removed. Studies have indicated that most of these would have been positive for HCV by PCR and thus infectious.²⁵

The prevalence of HCV in Canadian blood donations in 1993 was approximately 66 per 100,000.²⁶ According to the 1991-1992 Retrovirus Epidemiology Donor Study (REDS) database, the HCV prevalence in the United States was 218 per 100,000 donations. In the REDS, 4 seroconversions were observed among 152,000 repeat donations (62,444 person-years), yielding an annual incidence rate of approximately 6.4 per 100,000. The incidence of HCV in Canadian repeat blood donors is not known.

At present, version 2.0 of HCV antibody testing is in use in the blood system. The sensitivity of this test is in the neighbourhood of 95%. While it is impossible to

ascertain precisely the number of HCV-positive donations escaping detection in the Canadian system at present, some estimates are possible after certain assumptions are made.

Since the prevalence of HCV in Canadian blood donations is one-third that in blood donations in the U.S., one might extend this same proportion to incidence and assume that HCV incidence is in the neighbourhood of 2 per 100,000 repeat donors in Canada. Assuming a sensitivity of 95% and a relative risk of 5 between first-time donors and repeat donors (based on relative prevalence and frequency of repeat donations), then the average numbers of HCV positive donations escaping detection in the Canadian system can be estimated. Table 6 shows the range in estimates based on differing assumptions for the length of the HCV window period and the sensitivity of the test system.

Table 6
Estimates of the numbers of HCV-positive donations escaping detection

WINDOW PERIOD	95% SENSITIVITY	99% SENSITIVITY
2 weeks	26	6
1 month	27	7
2 months	29	9
3 months	31	11
4 months	33	13
5 months	35	15
6 months	37	17

Under these assumptions and with a test sensitivity of 95%, the number of HCV-positive donations currently escaping detection is in the neighbourhood of 26 to 37, depending on the length of the window period. As can be seen in Table 6, the primary contribution to residual risk is prevalent cases of HCV escaping detection due to the relative insensitivity of the current test system (group II error). There are third generation HCV antibody tests, which have greater sensitivity; these should further improve the safety of the Canadian blood supply with respect to risk of HCV transmission.

There has been considerable discussion about the use of surrogate tests such as antibody to hepatitis B core antigen (anti-HBc) and alanine aminotransferase (ALT, also known as alanine transaminase) to identify donations at increased risk of causing

non-A, non-B hepatitis in recipients. This discussion was pertinent before the advent of screening for anti-HCV. There is no discernable advantage to be gained from use of these surrogate tests in the presence of anti-HCV screening that is currently in place.²⁷

Intensive donor screening may further reduce the risk of HCV-infected blood entering the system. For example, studies have found strong associations between HCV positivity and previous use of injection drugs and receipt of blood and blood products.²⁸ These findings once again underscore the need for intensive donor screening.

Hepatitis B virus

Hepatitis B virus (HBV) is a common cause of acute and chronic liver disease with worldwide distribution. Is transmitted by blood and other body fluids such as semen, cervical secretions and wound exudates. Chronic HBV infection occurs in 6 to 10% of cases and these are at increased risk of liver failure or hepatocellular carcinoma in 15 to 20 years.

Tests for HBV carriers are done on all donated blood, using a system that detects the presence of hepatitis B surface antigen. The test is designed with such high sensitivity for the presence of the antigen (0.3 picogram per ml) that the residual risk of HBV transmission is extremely low. The prevalence of HBV in Canada in 1993 was 30 per 100,000 donations.²⁹ In the U.S. the prevalence is 50.7 per 100,000 donations,³⁰ and there is a reported annual incidence of 28 per 100,000.³¹

Other transmissible diseases

There are other infectious agents that have blood phases, some of which are long enough to pose a potential risk for transfusion-associated infections. Many of these agents are endemic in other parts of the world. With changing patterns of immigration, refugees and increased travel, the prevalence of these infections could become important to the safety of the Canadian blood supply.

Chagas' disease: Chagas' disease is caused by infection with the parasite *Trypanosoma cruzi*. The parasite is endemic in Mexico and Central and South America and is transmitted by an insect. There is a high level of parasitemia during the acute infection, which commonly occurs in children, but low levels of parasitemia occur in chronically infected individuals. Serologic tests are available but the sensitivity and specificity of these tests are not well defined. Decisions about

screening blood donors must be based on the prevalence of antibodies in blood donors in Canada who have lived in endemic areas, particularly in rural settings.

Malaria: Malaria is endemic in many tropical areas of the world. It is caused by any one of four species of the plasmodium parasite. The parasite replicates in red blood cells and is usually detected by direct observation of blood smears. Antibody tests are available but are not helpful in determining whether someone currently has parasites. The current practice is to exclude donors who have travelled to, or are recent immigrants from, endemic areas.

Erythema infectiosum or fifth disease (caused by parvovirus B19): Parvovirus is probably spread by respiratory secretions and rarely by blood. In erythema infectiosum, the virus is present in the blood for only a few days before the onset of symptoms. Patients with aplastic crisis (usually limited to individuals with underlying red cell abnormalities such as sickle cell disease) are viremic for a longer period, from a few days before symptoms until one week after onset of symptoms. The prevalence of antibodies is about 5 to 10% in young children and increases to about 50% in adults. The presence of antibodies generally indicates that the virus has been cleared from the blood and there is no good evidence for a chronic carrier state in otherwise healthy individuals. As a result, antibody screening serves no useful purpose.

Lyme disease: Lyme disease, caused by the spirochaete *Borrelia burgdorferi*, has been described in many parts of the world. The organism has a blood phase which may be intermittent over a period of several weeks. However, transmission by blood transfusion has not been documented. Antibody tests are being standardized and interpretation of results is in transition. Donor screening does not appear to be necessary.

Yersinia bacteremia associated with blood transfusion: Bacterial infections are a rare complication of blood transfusion. In a four-year period, 10 cases of Yersinia sepsis were reported in the U.S. with seven deaths, and five cases were reported outside the U.S.³² These cases appear to be associated with bacteremia in the donor, although in most cases the donor was apparently asymptomatic. Transmission is associated with units stored for prolonged periods (mean 28 days) at 4°C. Donor screening is not helpful.

Transmissions relevant to immunocompromised recipients

There are other infectious agents that have a blood phase but most do not pose a risk to healthy people. For example, the herpes family of viruses establish persistent

infections but of these, only cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6) persist in peripheral blood lymphocytes.

Transfusion-acquired CMV is known to cause life-threatening infections in immunocompromised hosts such as transplant recipients and premature newborns. About 50% of donors have antibodies to CMV, indicating the presence of the virus. Consequently, a proportion of donated blood is screened for CMV antibodies to provide a supply of CMV-negative blood for transfusion to these special cases. In addition, removal of white blood cells further reduces the risk of transmission of CMV in these situations.³³

4.7.2 Immunologic risks of blood transfusions

The majority of blood transfusions are allogeneic, that is, the donor and recipient are different people and are therefore immunologically mismatched. The most serious risk is the result of transfusion of red cells that have major incompatibility with antibodies present in the recipient's blood. Occasionally, in these circumstances, death can occur. Statistics Canada figures for 1989 to 1991 show that 22 deaths were attributed on death certificates to transfusion reactions but this may be under-reported. Transfusion of blood with minor incompatibilities occurs more frequently, but rarely with serious results.

Significant controversy has arisen about whether blood transfusion increases the risk of cancer recurrence and whether the risk of post-operative infections is greater in transfused patients than in those not transfused.³⁴ These risks are incompletely characterized, but if they prove significant, it is most likely that they are mediated by the immune system.

Immunologic risks, especially hemolytic transfusion reactions, can only be avoided by either not performing the transfusion or by carefully controlling the systems that deliver blood components to recipients.

4.7.3 Lack of potency

When blood components lack potency, for example, when there are a suboptimal numbers of platelets per unit, recipients may be subject to adverse reactions, such as bleeding or anemia. Furthermore, patients who receive components lacking potency may require further transfusions. Data are not available concerning the frequency of adverse effects from components that lack potency. Blood centres are embarking on statistical process control to assure potency of blood components.³⁵ Additional controls will be instituted in blood centres in the future.

4.7.4 Adequacy of blood supply

A significant risk to patients could occur if supplies of blood components were insufficient to meet the needs. Demand for commercial fractionation products has been met by imports. Blood donations have declined in Canada since 1991 and continued decline is projected. Yet the number of patients transfused has remained and will likely remain constant (see Figure 6). Changes in ordering practices have resulted in fewer transfusions per patient episode. It is hoped that the current trends in donation collection are paralleled by reductions in inappropriate utilization. It would be a public safety issue if the blood supply could not sustain appropriate utilization of blood and blood products. Dr Aye, National Director of CRCS Blood Services, said in 1994 that it is becoming increasingly difficult to meet collection goals. Whether this recruitment difficulty is due to overall distrust of the blood banking system, fear of contracting AIDS by donating blood, or other unidentified factors remains unknown. Issues of donor recruitment, screening and retention are discussed later. However, if the current trends in utilization reflect a move to more appropriate use of blood and blood products, then the current decline in blood collected may not be a problem.

PART 5 Evaluation

5.1 Introduction

The committee assessed the safety of the blood system by considering utilization (ie, exposure to risk) and assessing the effectiveness of the quality assurance and continuous improvement of the manufacturing process. Eliminating over-utilization, for example, addresses all sources of risk. Biological risks such as contamination or deterioration of blood products are best reduced by quality control and continuous improvement of the manufacturing process. Risks of infectious diseases are most effectively addressed by improved donor screening and testing procedures, including GMPs for performing the test, labelling and lot release procedures. Although designed to improve overall quality, GMPs for actual component manufacture are unlikely to decrease the risk of infectious disease transmission significantly. Risks from new infectious diseases and inadequacy of the blood supply are primarily reduced by improving the governance, direction, planning and process management of the blood system.

As the work of the committee proceeded, attention focused on findings, issues and recommendations. In this section the committee presents findings, both overall and specific.

5.2. System governance and funding

As described in the functional model, the responsibility for making decisions on behalf of the Canadian population is the function of governance. With the present blood system, it is unclear where this overall authority resides. The subfunctions of regulation, as well as funding and priority-setting are vested in different institutions.

The CBA is responsible for transferring money from the provinces and territories to the national blood program. The governance function for the national blood program is the responsibility of the voluntary board of the CRCS, which has no direct accountability to taxpayers. The CRCS has traditionally taken responsibility for planning, subject to funding. Although the CBA has no authority for planning, it has significant leverage through its control of funding and its interest in efficiency.

At some point in the governance of a system, benefit-risk-cost decisions have to be made. The issue of particular relevance to the committee was whether decisions to introduce changes to the system to improve safety are made with the full knowledge of

the cost-benefit implications and the alternatives. There has to be direct accountability for those decisions and, as noted in the description of the functional model, public input.

Overall finding

The committee found evidence of major problems with the current governance. Neither the structure nor process clearly focuses responsibilities and relationships. Moreover, the leadership of the CBA and CRCS are adversarial.

Specific findings

- **No legislation, contract or other document clearly assigns responsibility for the management of the Canadian blood system. Responsibility and authority are unclear and diffuse.**

Although the CBA clearly believes it has a mandate from the health ministers to direct the Canadian blood system, the CRCS does not agree.

- **The CBA and CRCS do not agree on the interpretation of two key principles for the Canadian blood system as established by the territorial and provincial Ministers of Health in 1989.**

Through testimony and in face-to-face meetings with CBA and CRCS, disagreement emerged concerning the first principle of national self-sufficiency in blood and plasma collection (see Appendix XI). CBA has taken the position that it makes no difference where plasma from Canadian donors is fractionated; however, the CRCS believes its mandate is to manufacture derivatives in Canada.³⁶ The second principle about which they disagree is that safety of all blood components and plasma fractions should be paramount. The CBA believes a safety measure must be proven to be cost effective for implementation. The serious underlying issue is the lack of a mechanism within the current system to resolve such differences in interpretation.

- **The planning, priority-setting and funding functions of the Canadian blood system are diffuse and poorly developed.**

The committee found little evidence of focused short- or long-term planning, even in the funding arena.

- **The adversarial relationship between CBA and CRCS hinders communications and problem solving.**

Several examples are illustrative.

- a) the controversy between CBA and CRCS about building a plasma fractionation plant in Canada
- b) discord over the planning and development of the CISCO computer system by ETCOM, a development that was recommended by the BoB
- c) conflict over funding the implementation of good manufacturing practices
- d) disagreement over implementation of new technology, eg, exchange of letters about Nutricell.

During the deliberations of the committee, animosity between CBA and CRCS leadership was evident. This animosity is destructive to sound governance of the Canadian blood supply system.

- **The CRCS and CBA need to foster public awareness jointly and to maintain confidence of the Canadian people in the safety of the blood supply.**

The recent negative press coverage of the blood supply system has eroded public confidence. This has not been helped by the response of the agencies, for example, the delay in the release to the public of the USFDA's inspection findings from the Toronto centre. If the incident had been managed jointly and proactively by the participants, the negative impact could have reduced.

- **Little evidence could be found that the system has developed a coherent crisis management strategy.**

Current mechanisms for identifying and responding to indications of emerging threats to the safety of the blood supply are ad hoc. For instance, the reporting of infectious diseases is passive and local. There does not appear to be any single agency or policy that takes responsibility or control when rapid response is required.

5.3 Regulation

The committee based its evaluation of regulatory systems on the information gathered from reviews of the operations of the departments of government (specifically the Bureau of Biologics of the Drugs Directorate of Health Protection Branch of Health Canada). Evaluation was also based on documents, including inspection reports and submissions for plasma derivatives and blood components, and finally communications with personnel in the relevant sections of the Bureau of Biologics.

Overall finding

The Drugs Directorate has not taken a leadership role.

Specific findings

- **The regulatory framework for protecting safety of the blood supply is incomplete.**

Although the Act covers safety in a generic manner, there are no regulations governing blood collection or processing for blood components. The regulations covering plasmapheresis are out-of-date. Certain tests are specified, such as those for syphilis, but other more recent important tests, such as those for HIV and HCV, are not mentioned. The Good Manufacturing Practices, which are guidelines used for manufacturing drugs, do not legally apply to drugs on Schedule D, which are biologics. However, as there are no equivalent guidelines for biologics, the drug practices are used as guides.

- **The Bureau of Biologics is under-resourced.**

This finding is supported by the following:

- a) The recent explicit inclusion in 1989 of blood under the Act has necessitated increased resources, organizational change and more expertise. The Bureau of Biologics, charged with the responsibility of administering the legislated requirements for blood and blood products, as well as other biological drugs, does not have adequate resources or personnel.
- b) A great deal of staff time is being taken up in committee work for implementation of the Gagnon report.³⁷ The Gagnon report made 152 recommendations for a new more efficient model for the drug review process.
- c) Expertise developed within the bureau or directorate is often lost and difficult to replace.
- d) New staff being brought in are at entry level and require training and time to develop expertise in all aspects of the bureau's functions.
- e) The amendment to the Act (which added blood to Schedule D) indicated yearly inspections. This has not occurred and enforcement of the Act, at least until 1994, has been ad hoc.
- f) Centres have experienced significant delays in receiving inspection reports.
- g) There is no mechanism of grading deficiencies, so that those critical to safety are given higher priority.
- h) Follow-up on the deficiencies found in inspections has been inconsistent. The process is not formalized or consistent. The bureau has often relied on information from the centres that deficiencies were corrected.

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- i) The guiding philosophy for the bureau has not been clearly enunciated, ie, whether its role is to police or to facilitate. This is illustrated by the bureau's inconsistent approach to whether it gives advance notice of inspections.
 - **The review process for licensing blood products is adversely affected by lack of leadership and resources.**

There are long delays in the approval of new products. As a result the provision for emergency drug release is used to excess. Even biologics with requests for fast-tracking are backlogged. (For a description of the drug review process, see part 3.2.1.) There does not appear to be a standard format for reviewing submissions, or for training reviewers; however, there are policies for determining what is acceptable and what is not.

There is a shortage of time, money and staff to do testing. Some products are assessed on protocol, that is by reviewing documents, while others are independently tested. Although this may be appropriate depending on the products, there should be a consistent approach and policy guiding these decisions. Similarly, lot-by-lot testing occurs more consistently for some products than others. No component testing is performed.

The present staff structure of the Bureau of Biologics is quite fluid and individuals often perform tasks both within their respective sections and in other sections. The same people may be responsible for different aspects of the review and testing process. This has advantages if there are sufficient resources.

- **There are areas where regulatory authority is split and there is potential for duplication of effort.**

The diagnostic kits that are used to test blood for infectious disease markers are regulated under Medical Devices Regulations, administered by the Bureau of Medical Devices in another directorate, the Environmental Health Directorate. (See organizational chart of Health Canada in Appendix VIII.) However, as part of the process of licensing, the blood bank section of the Bureau of Biologics has to assess the adequacy of the diagnostic kits used by the regional centres of the Red Cross.

The Bureau of Biologics does not inspect the National Testing Laboratory of the Red Cross, where test kits are evaluated, although they do assess the process and have to approve the choice of the kits to be used at the centres. It does not appear that proficiency testing is required from the centres as part of the licensing process. It is required by some provincial legislation but it is not uniform across the country. Ontario has a laboratory licensing process, which involves detailed inspections.

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- **Communications are unstructured.**

Communications between the sections of the bureau are essential. As the number of staff increases, there will need to be operating procedures to ensure that the staff reviewing different aspects of the licensing process communicate their findings. Also, links with the Laboratory Centre for Disease Control need to be strong. Information on surveillance and monitoring is essential for rapid identification of potential or emerging threats to the safety of the blood system.

- **Very little research and evaluation is occurring that is specifically directed to factors affecting the blood supply system.**

There is very little research within the Bureau of Biologics. Any method development that is occurring happens in the Bureau of Drug Research. Active research and evaluation programs increase the opportunity to recruit and retain more highly qualified personnel and help staff to keep up-to-date with methods and emerging technologies. Such programs also have the ultimate value of identifying ways to improve the safety of the blood system. As there is very little funding directed to research, the opportunity for liaison with other researchers as outside experts is also limited.

Future direction

The bureau recognizes many of the difficulties and deficiencies and attempts are being made to rectify them. It is, however, unclear whether there is sufficient support from upper management and whether the required resources will be available.

Regulations for blood and blood components are being developed, as are GMPs for biological manufacturers. The use of regulations and guidelines has been inconsistent. The Act is general, while the regulations and guidelines deal with specifics and standards. However, with rapidly advancing technology specifics change rapidly. As the process of developing and promulgating regulations is slow, detailed specifications included in regulations are soon out-of-date. Therefore, performance standards in regulations can be supplemented by guidelines that contain the specifics for attaining the standards. Guidelines need to be developed, reviewed and updated in a process that involves stakeholders.

There is considerable expertise, experience and information on the latest developments outside the government. As good manufacturing practices are, essentially, international standards, the bureau can use these as a basis for review and determine whether they are acceptable standards for the Canadian jurisdiction.

The testing function of the bureau has not been critically evaluated. It is possible that some of the lot-by-lot testing could be reduced and the resources devoted to testing new products being introduced into the system. It is understood that the manufacturers often have highly sophisticated equipment for testing that may not be available to the bureau. Although there is considerable value in detailed protocol review, total reliance on this means of assessment is not sound.

5.4 Blood supply subsystem

The committee's evaluation of the manufacturing process of the blood supply system was based on information gathered from site visits to several regional blood centres, reviews of inspection reports from the BoB, USFDA, internal audits, and inspections by international experts commissioned by the committee. Although an overall basic level of safety and security was confirmed, numerous points for improvement were noted.

Overall finding

The critical processes are, essentially, in control because they are managed by dedicated and knowledgeable staff. However, the system is vulnerable to specific deficiencies that, left unattended, will compromise safety.

The manufacturing processes are very dependent upon the knowledge, training and commitment of the staff. The overall summary report submitted by the international auditors states:

A number of important GMP non-compliances were recorded on each site. However, there was clear evidence that, for those systems that were considered absolutely crucial, ie, collection, testing and release, the sites visited had secure (often manual) systems that ensured the provision of a safe blood supply.

Deficiencies are documented in detail in Appendix VI and are graded according to the degree of concern and potential for affecting safety. The principal and other major matters of concern mentioned in Appendix VI form the basis for the overall findings. Those classified as other points of concern are presented as opportunities for improvement. The importance and number of these often highly specific points is an indication that the process of implementing quality programs is long and difficult. Continual improvement is a goal of all quality systems. However, the specific points also have to be viewed as indicators of whether the systems are in control. These points will often function as early warnings of potential for larger problems that could pose a significant threat to safety, either of the system in general or to an individual patient.

Specific findings

- **The dedication of personnel in the blood centres is very high.**

Low turnover and staff dedication in the blood supply subsystem are impressive. The committee observed a culture of responsibility during all visits and inspections of blood centres. The quality and dedication of the staff in blood centres are holding the system together, despite severe problems identified below. To quote the international auditors:

Throughout the audit process it was abundantly clear that the Canadian Red Cross Blood Transfusion Services are fortunate to employ so many quite excellent staff, well motivated staff who were, in spite of the present difficulties, eager to do a good job and keenly interested in how they could do it better.

- **Personnel working in the blood centres are under considerable stress. If this problem is not addressed soon, it could jeopardize safety.**

There are two major sources of stress for the personnel working in the blood centres. The first is the loss of public confidence in the system. The second is the rapid rate of change imposed on the system. Although rapid change is the rule rather than the exception in every domain these days, the Canadian blood system is under more pressure than most because it has fallen behind in key areas such as the implementation of GMPs and integrated information systems. Although staff morale appeared satisfactory, staff were quick to point out concerns over the rate of change. As the pressure to catch up increases (ie, to meet USFDA requirements and implement GMPs and a new computer system) this problem will get worse before it gets better. The recommendations of this study will inevitably add to that pressure.

- **Although personnel are working hard to implement state-of-the-art quality systems, including GMPs, there are major impediments to overcome.**

Based on visits to National Office and various regional blood centres, the committee was convinced that the importance of implementing quality programs using GMPs was recognized and that personnel were working diligently at upgrading the current operations to state-of-the-art manufacturing practices. However, the CRCS had fallen behind in this area and it cannot catch up without allowing a minimum of time for people to absorb change. The implementation of quality processes based on GMPs requires profound changes in the working culture that cannot be accelerated beyond a certain point, even if resources are unlimited.

The international auditors noted a number of impediments to progress in implementing organization-wide quality programs.

- 1) **Lack of clear objectives and standards.** Staff were unclear as to which standards they should follow: BoB, National Office, or USFDA. The reports contain evidence of inconsistencies that led to confusion.
- 2) **National Office.** SOPs, directives and policy setting. A particular concern noted was "unreasonable demands for rapid, excessive and, at times, ill-conceived change." At various points the auditors recorded indecision, delay and a complete lack of communication from the National Office. As the auditors found differences in the systems at the three sites visited, they questioned the policy that controlling operations through National SOPs would produce a generic system.
- 3) **GMPs.** Concern was expressed that the overall comprehension and implementation of systems were in very early stages. Among the issues cited were the insufficient training, knowledge, responsibility and authority for the QA specialists to function as QA managers in a GMP environment. Of particular concern was the plan to change the reporting lines from centre director to National Office. They also thought there was too much emphasis on "inspecting out" errors and too little on prevention, ie, that quality was not being designed into the system. They concluded that this indicates that error management systems need improvement.
- 4) **Computer systems.** The lack of an effective, fully integrated computer system was a major concern (see Appendices VI and IX and below).
- 5) **Finance.** Overall, there was concern that lack of money was preventing GMP compliance. Several examples are cited in the reports in Appendix VI, including outdated equipment, poor facilities and inadequate cleaning and maintenance.

The committee agrees with this assessment.

- **A serious deficiency in the Canadian blood system is the lack of integrated data management systems.**

As the processes involved with the blood system become more complex and steps are added to promote safety, the opportunity for human error increases. At present, various steps are checked and vital processes are double-checked by different staff to detect errors. This system is laborious and not foolproof. There is potential for error in such important processes as duplicate record checking, recording transmissible disease testing results, labelling and product release. Duplicate records on donors are of particular concern. Such incidents have been described in the accident and error reports to the Bureau of Biologics. Lack of a national integrated donor database and reliance on manual checks of donor status can result in failure to detect previously deferred donors. This adds unnecessarily to the residual risk in the blood supply.

The only data management system currently being used on a national basis is BLIS (Blood Information System). The CRCS recognizes the severe limitations of this

system. Principal among the concerns observed at all audits and inspections are the relatively open access to the system, lack of protection of confidentiality and the potential for error in duplicate records and altering (updating) deferral codes. Guidance provided by National Office was a programmer's guide, found to be of little use to hands-on users.

Blood centres that are considered to be state-of-the-art employ data management systems that minimize clerical error in the manufacture of blood components by minimizing manual steps in data management. The key features of these systems include:

- 1) integrated donor, testing and final release databases with information capture at each stage of the manufacturing process
- 2) positive sample identification systems at all stages of production
- 3) electronic laboratory data interface without a manual step.

- **As of 1 June 1994, the data management system under development for the Canadian blood system exhibits several important shortcomings.**

During a site visit to the Edmonton centre, the CISCO information management system under development for the CRCS was reviewed and several important areas for improvement were found (see Appendix IX).

Of major concern was the fact that laboratory data were not interfaced with donor unit management systems. Other areas requiring improvement are:

- 1) A robust method had not been developed to resolve the possibility of duplicate donor records.
- 2) The menu-driven architecture was labour intensive and not user friendly.
- 3) Systems are not secure; donor data was available to those with no need to know
- 4) Although the project was still at the pilot-testing phase, the committee found that much of the training materials and planning for implementation were incompletely developed.

Despite these shortcomings, which can and should be addressed, the concepts on which the CISCO information management system is based were considered sound.

- **Planning and management are needed to support system change.**

Change management is of critical importance, especially in this time of intense flux. The committee found that the Canadian blood system is not coping with such change as well as it should. This evaluation is based on a series of observations:

- The committee could not find an articulate financial plan for the operation and upgrading of the blood manufacturing and distribution

operations in Canada over the next two to five years. It could not find practical cost data on which such a model could be based. For example, figures on the production costs for the various types of blood products were not available.

- The committee thinks that the fact that blood centres lack adequate integrated information management systems at this date is due not to lack of funding or information technology skills but to inadequate planning and project management.
- Personnel in various blood centres expressed concern that sufficient resources are not available to implement new systems and procedures such as GMPs. The committee did not find evidence that the cost of change had been properly evaluated and presented to provide adequate support for the priority-setting and budgeting process. For example, resources are needed for the increased training that is needed to implement GMPs.
- In many cases personnel in the centres play almost no role in developing and implementing new systems and procedures. Although some mechanisms exist for field personnel to test new systems and procedures, in many cases the people responsible for implementing these new systems and procedures hear about them only when everything has been decided, including the implementation date. As a result, 1) the new systems and procedures often have to be adapted, 2) personnel in centres have limited knowledge and understanding of the changes about to be required, 3) personnel do not have the opportunity to "buy into" the process, and therefore have greater resistance to the changes and, 4) the implementation plans are sometimes not realistic and could result in system failure.

5.5 Utilization

Overall finding

A major reduction can be achieved in the utilization of blood and blood products. Elimination of unnecessary blood use offers the greatest potential for reducing public exposure to risk in the system.

Unnecessary transfusions confer risk but no benefit. Elimination of unnecessary transfusions will reduce all transfusion-associated risks in direct proportion to the decrease in utilization. The risk is reduced for infection with HIV, HCV and all other

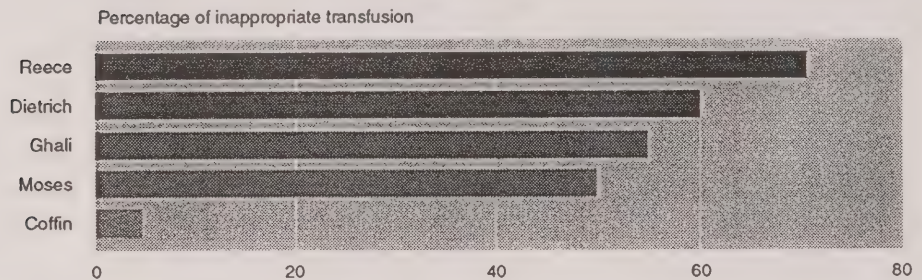
pathogens, even those not yet identified, as well as for risks through system and subsystem errors. Reducing utilization to appropriate levels offers the potential for the greatest reduction of risk in the Canadian blood system. Evaluations of red blood cell transfusion practices indicate that a significant proportion of transfusions in Canada could be avoided through: implementation of clinical guidelines, linking the cost of blood products to hospital budgets, public education and informed consent, improved surgical techniques and increased use of recombinant and synthetic products. These strategies are discussed in more detail below.

Specific findings

- **A substantial proportion of red blood cell transfusions are unnecessary.**

Studies estimate that the proportion of inappropriate red blood cell transfusions is as high as 67% (see Figure 4).³⁸ The range in estimates is largely due to the use of different preset criteria to assess transfusions.³⁹

FIGURE 4
Studies assessing red blood cell transfusion practices



The only study that found utilization to be within acceptable limits used loose criteria. In contrast, a recent study by Ghali at a teaching hospital in Canada⁴⁰ using published guidelines from the American College of Physicians, found that 55.3% of red cell transfusions were unnecessary.⁴¹ There is a declining trend in red cell transfusions. However, unnecessary red blood cell transfusions are likely occurring in hospitals across Canada.

- **Systematic transfusion audits in hospitals, linked with specific feedback to physicians and education programs, and other utilization management techniques have received insufficient attention.**

Toy reviewed studies of the effectiveness of transfusion audits and practice guidelines for improving utilization.⁴² Transfusion audits can improve utilization when: 1) audits

occur in a timely manner (either before transfusion or during the 24 hours after), and 2) individual education of ordering physicians is provided by transfusion medicine specialists.

Figure 5 summarizes results from studies of the impact of physician education on reducing the number of blood units transfused. Physician education typically consists of disclosing audit results, reviewing practice guidelines, and case presentations. Following physician education reduction in utilization of fresh frozen plasma ranged from 46% to 77%.⁴³ Reduction in platelet use ranged from 14% to 56%. Table 7 describes key findings from three studies showing the effectiveness of physician education for producing significant decreases in inappropriate transfusions.⁴⁴ Taken together, these studies indicate that physician education and transfusion audits can produce a significant decrease in inappropriate utilization.

FIGURE 5

Impact of Physician education and audits in reducing blood transfusions

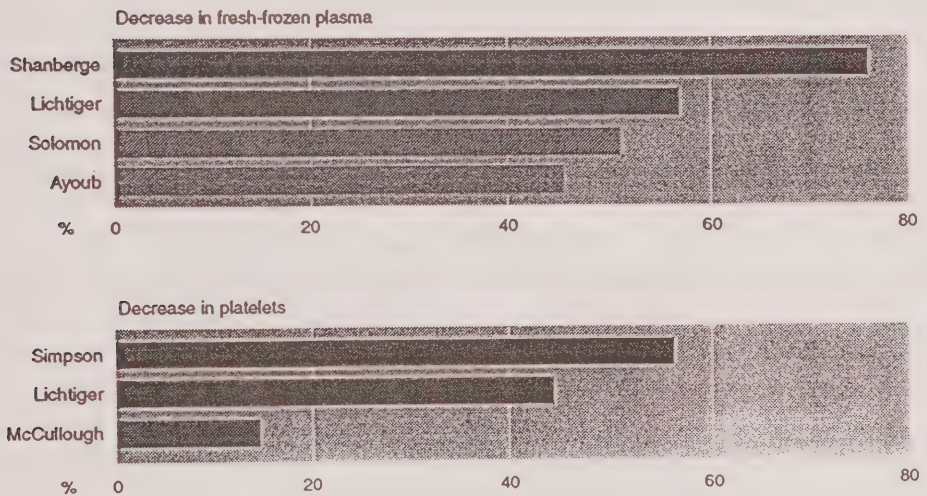


Table 7

Reduction in inappropriate units transfused following physician educational aid audits

STUDY	FINDING
Renner (1987)	decrease in episodes failing to meet screening criteria from 3.2% in first two-quarters to 0.5% in last two-quarters of review year
Giovanetti et al. (1988)	reduction in over-transfusion units from 37% to 10% over two years
Barnette et al. (1990)	decrease in inappropriate fresh frozen plasma transfusions from 53% (baseline) to 22% after education

- **There is insufficient research on the effectiveness of alternative strategies for reducing utilization in the Canadian blood system.**

More studies in Canada are needed to provide estimates on the rates of inappropriate transfusions, as well as the value of the broad implementation of preset criteria for transfusion practices (such as the American College of Physicians Guidelines). Parallel studies are needed to determine the degree of inappropriate use of plasma derivative products. For example, there has been an increase in the use of albumin over the past decade, so that it has outstripped the collection of plasma units. This has contributed to a decrease in plasma self-sufficiency from 90.0 % in 1984 to 69.6 % in 1993/94.

The following strategies could have significant impact on reducing over-utilization:

Clinical guidelines and physician education: Preset criteria and clinical guidelines for red blood cell transfusion and use of blood products have been developed but not yet adopted by the provincial medical associations and licensing boards. A study of local area variations could promote more consistency between and within hospitals and clinical departments. High priority must be placed on ensuring that each hospital has in place a process for individual physician education provided by transfusion medicine specialists and timely feedback from audits to ordering physicians.

Costs apparent to users: Currently, blood products are provided free to hospitals and physicians. There is no system for charging hospital budgets (similar to drug costs) that makes the actual cost directly apparent to users. Such a practice could lead to a more stringent focus on blood product utilization, similar to utilization reviews and controls on drug therapy.

Specific informed consent: Requiring informed consent for red blood cell transfusion and use of blood products would mean that individuals are provided with the information necessary to assess the potential risks and benefits. This could also stimulate health professionals to carefully consider, in each case, whether the blood product is absolutely necessary.

New interventions and technologies: The development of improved surgical techniques and intra-operative salvages is tending to lower the need for red blood cell transfusion. Recombinant and synthetic replacements for blood and blood products are being developed. Such products could decrease the need for transfusions and decrease risks of transmitting blood-borne transmissible diseases. However, it should not be assumed, automatically, that these will always be safer. Like any new technology or drug, such products need careful and thorough assessment of the risks, benefits and efficacy.

5.6 Donor recruitment, screening and retention

The donor recruitment, screening and retention program has several critical control points that are vital for ensuring safety of the final blood products. The first is the need for a stable, well-characterized donor base. To the extent that the "upstream" collection component is successful in excluding donors whose blood may transmit diseases to recipients, the "downstream" safety of blood products is greatly enhanced. However, for the critical control point of donor exclusion to be effective, it is essential that potential donors fully understand whether their donations may present transmissible disease risks, and that they report truthfully and accurately during the health assessment.

General finding

The safety of the blood system depends directly on the extent to which it can rely on a stable, well-characterized donor pool and can effectively exclude donors who may pose a risk.

During the past five years (1989-1993), there has been a 12.6% decrease in the number of donations and this decrease is expected to continue (Figure 6). However, there has been a parallel decline in the demand for red blood cells for transfusions, which may be appropriate (see discussion on utilization in Part 5.5). Thus, overall demands continue to be met except for occasional shortages of specific blood types. On the other hand, the Canadian system is not able to maintain self-sufficiency with respect to some plasma derivatives. For example, self-sufficiency for producing albumin has fallen to less than 70% in 1993-94 (Figure 7). However, this has been accompanied by a marked rise in the utilization of albumin, and the appropriateness of this increased use requires investigation.

FIGURE 6
Trends in donation and transfusion needs

Estimation based on 1989/1993 data

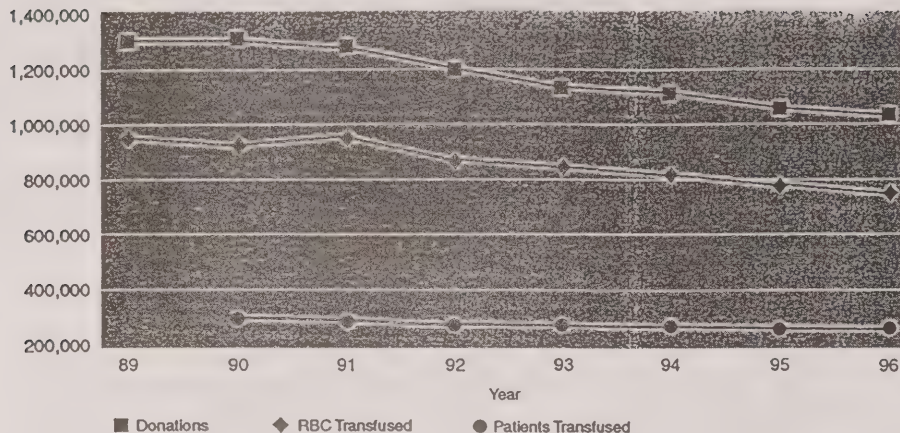


FIGURE 7
Plasma self-sufficiency

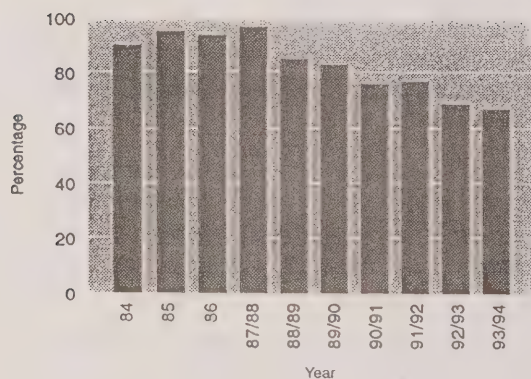
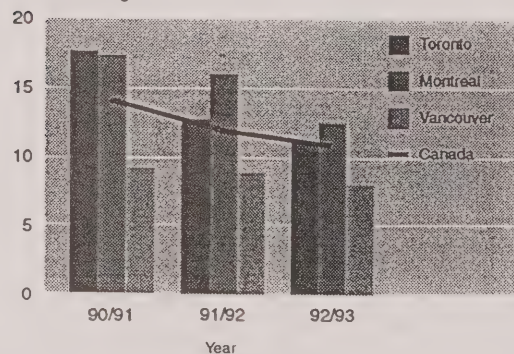


FIGURE 8
Declining trend in new donors

Percentage of New Donors



To maintain a stable, well-characterized blood supply, new donors must be continuously brought into the system. There has been a decline in the number of new donors as shown in Figure 8. While there is some benefit in relying less on first-time donations because of their disproportionate contribution to residual risk (see below), the blood system needs to attract and retain donors at levels sufficient to support appropriate utilization of blood and blood products.

- **There is no standardized approach to donor recruitment.**

There are no SOPs for donor recruitment or a comprehensive national strategy.

- **No systematic efforts are made to determine whether donors truly understand the screening questions and educational material regarding risks.**

At the time of registration, prospective donors are given pamphlets regarding risk activities and circumstances that should cause them to refrain from donating. However, the current system is passive with respect to detecting whether the prospective donor actually understands the information. Nurses confirmed that they do not probe enough to ensure that the prospective donor understands the pamphlets or specific questions on the health questionnaire, and therefore they may not know if the donor understands. In addition, no standard procedure is evident for screening prospective donors regarding their reading level and language comprehension.

A proposed new screening process being pilot-tested by the CRCS includes specific questions and probes to assess whether the prospective donor has read and understood all information, and whether all the questions the donor might ask have been answered. Also, the new format includes specific questions about participating in risk behaviours. Such an approach has been shown to increase effectiveness of screening out at-risk donors.⁴⁵ High priority should be given to the nationwide implementation of this new protocol for donor screening.

Computerized screening could include a health information module with graphic aids that would both enhance and assess the likelihood that prospective donors understand all information. A systematic procedure could be put in place that would identify cases where the prospective donor may need help in reading and understanding the information and screening questionnaire.

Studies on the effectiveness of computerized screening in blood banks have been conducted in the United States by the American Institute for Research (1993).⁴⁶ The AIR study found that when a computer interview was conducted first, more subjects were deferred than when the current interview was conducted first. A recent

comparison of audio versus written questionnaires found that the audio version identified more HIV risk factors and had fewer missing responses.⁴⁷

The SOP for donor screening indicates that prospective donors are to be excluded if they are intoxicated from alcohol or drugs, yet research shows that even addiction specialists can have difficulty detecting whether a patient has been using alcohol.⁴⁸ Further attention must be given to staff training and screening procedures that are aimed at detecting high-risk behaviour related to injection drug use.

- **There is no process for reinstating donors who are deferred due to a repeat reactive test for a transmissible disease marker and are subsequently found to be negative.**

Reinstatement of deferred donors is a controversial issue. Several medical directors noted to the committee the need for a process to reinstate donors who are confirmed negative for transmissible disease markers. However, the process of donor reinstatement can only be undertaken when there is an integrated computer system in place to eliminate and prevent errors.

Although only a small proportion of the deferrals are for repeat reactive results for transmissible disease markers, the number is not insignificant. As the number of tests increases and there is an emphasis on sensitivity and surrogate tests, the specificity decreases and there are more false positives. An example of the effect of a change in specificity was the CRCs experience in 1993 when they moved to new versions of test kits for HTLV and HBsAg.⁴⁹ The number of repeat reactives for HTLV increased from 184 in 1992 to 3,099 in 1993, while the number of confirmed positives actually decreased from 46 in 1992 to 32 in 1993. Similar results were obtained for HBsAg. This meant that for the HTLV test alone, nearly 3,000 donors who were negative were permanently deferred. Not only does this become a significant issue for a declining donor pool, but there is considerable negative impact on donors who wish to donate and are told that their tests are confirmed negative.

- **Repeat donors are frustrated by the lengthy screening process, which repeats the same questions each time a donation is made.**

A common finding at blood centres is that repeat donors are frustrated by having to go through the same lengthy screening process each time they make a donation. A comprehensive study conducted by the American Institute for Research in 1993 concluded that there is sufficient justification for separate tracks for first-time and repeat donors. If repeat donors are spared the more intensive screening this would go a long way toward reducing frustration and potential loss of donors due to screening.

General finding

First time-donations (11% of total) contribute disproportionately to the residual risk from transmissible diseases.

Any consideration of safety within the Canadian blood system would be incomplete without an analysis of the degree of risk contributed by first-time donations. Therefore the committee analysed the Red Cross National Testing Laboratory data for 1993 (Table 8).⁵⁰

Table 8

Analysis of prevalence of transmissible disease markers by donation status (first-time and repeat donations) among 1,079,871 donations to CRCS in 1993

	First-time number (%)	Repeat number (%)	Total	Rate per 100,000 in first-time donations	Rates per 100,000 in repeat donations	Rate ratio (first-time to repeat)
HIV-positive	8 (42.1%)	11 (57.9%)	19	7.0	1.1	6.2
HCV-positive	358 (55.2%)	290 (44.8%)	648	313.9	39.0	10.5
HTLV-positive	20 (55.6%)	16 (44.4%)	36	17.5	1.7	10.6
HBsAg-positive	219 (69.1%)	98 (30.9%)	317	192.0	10.1	18.9
Syphilis-positive	34 (24.1%)	107 (75.9%)	141	29.8	11.1	2.7
Total donations	114,045 (10.6%)	965,826 (89.4%)	1,079,871			

In total there were 1,079,871 donations whose ballots were marked for transfusion. Of these, 114,045 (10.6%) came from first-time donors. However, first-time donations that were positive for various transmissible diseases were markedly out of proportion to their representation among all donations. First-time donations contributed: 42% of HIV-positive tests, 55% of HCV, 56% of HTLV, 69% of HBsAg and 24% of syphilis.

The right-hand side of the table expresses these same data in terms of prevalence rates per 100,000 donations. The prevalence of HIV among first-time donations was 7.0 per 100,000 donations compared to 1.1 for repeat donations. This represents a prevalence rate ratio of 6.2 for first-time donations relative to repeat donations. The

multiplicative increase of prevalence among first-time donations relative to repeat donations ranged from 2.7 for syphilis up to 18.9 for HBsAg.

It is important to note that all the donations identified in the table as positive for transmissible diseases were removed from the blood supply. The question remains, however, as to how much of the residual risk (ie, not detected and therefore still remaining in the system) is contributed by first-time donations. First-time donations will contribute to those donations that are missed due to test and system insensitivity and error, since the latter are proportional to the prevalence rate among donations. Thus, first-time donations likely account for 40 to 60% of this type of undetected positive unit.

The number of donors missed by the detection system because they were in the window period depends on the incidence rate. The ratio of incidence in first-time donors relative to repeat donors is not known. However, estimates are available for the ratio of prevalence rates. The calculated prevalence rate in repeat donors is not the same as the prevalence in repeat donations because the rate in repeat donors is not corrected to account for multiple donations. However, given a liberal estimate of about two donations per year, the prevalence ratios of first-time donors relative to repeat donors still range from 1.3 up to 9.5. It does not necessarily follow that the incidence rate in first-time donors is elevated simply because their prevalence rate is elevated. However, preliminary studies have suggested that incidence rates are indeed elevated in first-time donors relative to repeat donors. The REDS study in the U.S. has utilized estimates in the neighbourhood of 2 for this increase in incidence.

If this reasoning is valid, the relative contribution of first-time donors to residual transmissible disease risk would be similar to their relative contribution to detected disease risk. One may conclude that **first-time donors contribute approximately 11% of donated blood but contribute disproportionately to the residual risk due to transmissible diseases.** Therefore, first-time donations constitute a very important group in terms of potential risk reduction. This would be true of any identifiable subset of donations that constitutes 10 or 11% of the total and yet accounts for half of the residual risk. However, a blood system cannot operate without first-time donors. As repeat donors leave the donor pool for various reasons, they must be replaced by first-time donors in order to maintain a stable blood supply.

PART 6 Conclusions and Recommendations

Throughout its review, the committee could not find data from specific studies or other evidence to indicate that the Canadian blood system in 1994 is any less safe than blood systems in other developed countries. However this conclusion is made with the caveat that there are incomplete data on outcomes from use of blood and blood products. In the absence of specific studies in Canada (or any other country), assumptions about safety are based primarily on studies of infectious agents in donations and effective use of screening tests for these infectious agents. In the Canadian system data on donations and screening tests used do not suggest an increased risk to recipients of blood or blood products in Canada in 1994 compared to that in other developed countries.

In addition, the committee evaluated whether blood collection, manufacturing and product management operations at regional centres were of a standard to minimize risk of processing errors. The manufacturing practices and control systems were assessed during site visits and detailed centre inspections. The overall assessment was that the systems in place were satisfactory, yet fragile. This overall assessment was made taking into consideration the ability of the well-trained, meticulous and dedicated staff to cover the deficiencies identified.

Without being rectified, the deficiencies identified could seriously compromise safety. The committee's analysis led to the following recommendations, listed in order of priority.

Recommendation 1

Eliminate over-utilization of blood and blood products. Blood and blood products should be used only when clearly indicated.

Accumulating evidence indicates that as many as one-third to one-half of all red cell transfusions may not fall within accepted clinical guidelines and may not be medically necessary. Effective mechanisms are required in the current Canadian blood system to address the problem of over-utilization. The current funding system in which blood is provided at no charge to hospitals does not provide any direct incentives for utilization management. Mechanisms to reduce over-utilization include: 1) adhering to clinical guidelines and local utilization management, 2) making the cost of blood transfusions apparent to the users, 3) requiring specific informed consent from recipients for the use of blood and blood products within hospitals and 4) developing less invasive surgical techniques and using synthetic and recombinant replacement products.

It cannot be overstated that reducing transfusions by a given proportion will reduce all transfusion-associated risks by that same proportion. The risks are reduced for infection with HIV, HCV and all other pathogens, even those not yet identified, as well as for risks through system and subsystem errors. **Reducing utilization to appropriate levels will result in the greatest reduction of risk in the Canadian blood system.**

Recommendation 2

The Canadian blood system must be restructured to eliminate conflicts among the participants and at the same time clearly define responsibilities for the safety of the blood supply and the operations of the blood subsystem.

Safety of the Canadian blood system is impeded by its structure. Relationships between the participants – the CBA, the CRCS and the BoB – remain ill defined, and decision making regarding safety of the system is fragmented. The funding authority (CBA) is separated from the operations (CRCS), and the role of the BoB in protecting the safety of blood is incompletely developed. As a result, accountability and responsibility for system improvement have been diffused. The CBA appears to have been created primarily as a financial gatekeeper to control costs and the CRCS has historically been autonomous. As a result, the CRCS and the CBA are openly antagonistic. The committee found several examples where these governance difficulties adversely affected decisions about safety: eg, delay of funding for CISCO development, withholding funding for cGMP implementation and the Nutricell controversy.

Recommendation 3

The Bureau of Biologics (BoB) must take a leadership role in assuring safety of the blood supply. The BoB must be provided with sufficient resources for staff, testing and training to operate effectively.

The bureau should ensure that the following functions are in place:

- development of regulations specifically for blood and blood products
- development, in collaboration with stakeholders, of GMP guidelines specifically applicable to blood centres and processing blood components
- ensuring that regulations are strictly enforced through regular, comprehensive inspections with timely follow-up on deficiencies found
- development of mechanisms/plans for dealing with emergencies, crises and situations requiring immediate decision making and action
- development of mechanisms for monitoring and tracking local, national and international occurrences and trends for anticipating where action may be needed.

Recommendation 4

The Canadian Red Cross Society (CRCS) must continue to implement a strong quality program emphasizing good manufacturing practices and a total quality management approach to ensure continuous process improvement. The CRCS must develop or acquire an integrated computer system that includes a laboratory data management system.

The CRCS should continue implementing GMP programs in each centre, including developing a rational change management process. These efforts will require planning and availability of resources and must be endorsed and supported by all elements of the Canadian blood system. Continuous improvement programs should be developed as part of error management and to correct process weaknesses detected during internal audits.

Rapid deployment of a computer system accessible to each centre should be a high priority. CRCS management must decide, following external review, whether CISCO will offer the most rapid track to computerization of the blood subsystem, or whether alternative systems that can be installed rapidly should be explored. This decision should be made considering the risk inherent in the development of a complex piece of software. The system installed should include a laboratory data interface with other safety systems, such as the donor deferral registries, labelling activities and lot release. If the CISCO approach is retained, there must be a re-evaluation of the safety-critical software and the implementation plan to determine a means of accelerating it. The committee believes centre computerization is an important step in protecting the safety of the blood supply in Canada.

Recommendation 5

New systems for donor management are needed to ensure a stable, well-characterized donor base. Given the concentration of transmissible disease risk among first-time donors, implementation of a dual-track system should be evaluated, where repeat donors are given routine screening and first-time donors are given more intensive assessment.

The collection component of the blood supply system has several critical control points that are vital for ensuring safety of the final blood products. A stable, well-characterized donor base is critical for ensuring safety. The following options can lead to significant improvements in donor management:

- a) differential screening (dual track) whereby first-time donors (both new and infrequent) are given more intensive assessment and repeat donors are given routine screening
- b) reinstatement of deferred donors who are cleared
- c) enhanced and targeted donor recruitment strategies

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- d) redesign of the screening process for first-time donors with an evaluation of the effectiveness of pretesting a blood sample taken a few months prior to the first donation.

Recommendation 6

Comprehensive surveillance is needed to document infection and other adverse outcomes, so that threats to safety of the blood system can be assessed. Mechanisms must be put in place to ensure national reporting, international links, unified responsibility for analysis and clear authority for rapid response to indications of the emerging threats to the blood system.

Clearly defined policies and procedures are needed to govern roles and responsibilities in the ongoing surveillance of, and rapid response to, new pathogens and other potential threats to the safety of the blood supply. Current mechanisms are conducted very much on an ad hoc basis and include: informal affiliations and passive information from public health agencies in Canada and abroad, a number of different and potentially conflicting scientific advisory bodies, and reliance on individual decision making. There does not appear to be any single agency or policy that provides governance when rapid response is required.

Recommendation 7

Monitoring must be improved to include outcome analysis based on full tracking of units from donors through to recipients and outcome analysis.

Adverse reactions to transfusions are often difficult to identify, and unless serious, there is no requirement for reporting them. Monitoring and response to findings are mostly at a very local level and vary depending on individual hospitals. As a result, there are major deficiencies in the blood system with regard to monitoring outcomes among transfusion recipients and providing adequate follow-up of adverse effects.

There have been difficulties tracing donors and recipients of HIV-infected blood. Although it is possible for the CRCS to trace units from the donor to the hospital, and for the hospital to trace them to recipients, the process is cumbersome and labour intensive. The difficulty has arisen in part because hospitals and CRCS have circumscribed their own record keeping in isolation of each other. Proper monitoring can best be ensured by implementing a unified tracing system that follows each unit of blood from the donor, through the collection and manufacturing process, to the recipient. Such a system can maintain the highest standards of confidentiality and still provide the opportunity for both rapid and efficient programs for tracing back and for ongoing monitoring of outcomes among transfusion recipients.

Recommendation 8

An ongoing program of health systems, clinical and basic research is needed to ensure continual improvements to the blood system.

Research is essential to improvements in the blood system, many of which have important safety implications. At this time most research is investigator initiated. The funding comes from a variety of sources and there is no directed plan to evaluate and address the needs of the blood system as a whole, including health systems research. There needs to be a planned program for directed research to ensure adequate funding, to identify and establish priorities for areas of study and to integrate the results of studies. This should help to ensure that the studies will be incorporated into the planning, design and management of the system to improve its safety and security.

Studies and evaluations of all aspects of the system are needed, including:

- a) evaluations of systems management including studies on the effect of implementation of new systems on donor screening, efficiency, safety, worker satisfaction and so on
- b) studies on outcomes of blood and blood product use including active tracking of complications, ie, adverse reactions and infections
- c) development and testing of crisis management strategies including international collaborative research
- d) studies leading to the development of new technology relevant to practical aspects of blood banking
- e) basic science and medical research with short- and long-term relevance to the blood system and health care, eg, alternatives to blood and blood products.

Recommendation 9

Concerted action must be taken to rebuild the confidence of the Canadian public in the blood system.

It is not sufficient that the blood system be safe – it must also be considered safe. Public confidence in the Canadian blood system is now so low that it will require significant action to restore it. Together with other measures taken to improve the system, a concerted communication program must be initiated to rebuild public confidence as soon as possible. Otherwise, public mistrust will undermine efforts undertaken to improve the system.

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^b Appendix B and C to Carol Major's Report (Appendix III)

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ACRONYMS

AHF	Antihemophilic factor
AIDS	Acquired immune deficiency syndrome
AIR	American Institute for Research
ALARA	As low as reasonably achievable
ATGA	Australian Therapeutic Goods Association
ATL	Adult T-cell leukemia
BLIS	Blood Information System
BoB	Bureau of Biologics
BTS	Blood Transfusion Service
CAP	College of American Pathologists
CBA	Canadian Blood Agency
CBER	Center for Biologics Evaluation and Research (U.S.)
CCPs	Critical control points
CDC	Centers for Disease Control (U.S.)
cGMP	current Good Manufacturing Practice
CHS	Canadian Hemophilia Society
CI	Confidence interval
CISCO	Computer Information System for Centre Operations
CMV	Cytomegalovirus
CRCS	Canadian Red Cross Society
DB	Diagnostic biotechnology
DMS	Data management system
EBV	Epstein-Barr virus
EC	European Community

EIA	Enzyme-linked immuno assay
FFP	Fresh-frozen plasma
FTE	Full time equivalent
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAM	HTLV-I associated myelopathy
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-cell lymphotropic virus
ICL	Idiopathic C-D4 lymphocytopenia
IgA	Immunoglobulin A
IND	Investigational new drug
ISO	International Organization of Standardization
IT	Information technology
IVIG	Intravenous immunoglobulin
LCDC	Laboratory Centre for Disease Control
LPTP	Laboratory Proficiency Testing Program
MCA	Medical Control Authority (U.K.)
MIS	Management information system
NBSC	National Blood Services Committee
NDS	New drug submission

NTL	National Testing Laboratory
PCR	Polymerase chain reaction
QA	Quality assurance
QC	Quality control
RBC	Red blood cell
R & D	Research and development
REDS	Retrovirus Epidemiology Donor Study
RFP	Request for proposal
RIBA	Recombinant immunoblot assay
SOPs	Standard Operating Procedures
TDL	Transmissible Disease Laboratory
TQM	Total quality management
TSP	Tropical spastic paraparesis
TTD	Transfusion transmissible disease
UBMDR	Unrelated Bone Marrow Donor Registry
USFDA	United States Food and Drug Administration
WHO	World Health Organization

GLOSSARY

Albumin

A plasma derivative. It is the protein found in the highest concentration in human plasma.

Alpha IX SD

High-purity factor IX used in the treatment of hemophilia B or Christmas disease.

Antigen

A substance that is recognized by the body as being foreign, thus it can elicit an immune response. In blood banking, antigens are usually, but not exclusively, found on the blood cell membrane.

Antihemophilic factor (AHF)

Blood coagulation factor VIII.

Apheresis

The process in which blood is removed from an individual, anticoagulated and separated into specific components. Once the components have been separated, any component can be withdrawn. The remaining portions of the blood are then remixed and returned to the donor.

Aplastic anemia

Anemia caused by deficient red cell production due to disorders of the bone marrow.

Autologous donation

The donation of blood by patients for transfusion to themselves in the future.

Blood Information System (BLIS)

Computer system currently used by the CRCS.

Blood Services

Department of the CRCS committed to delivering blood and blood products to Canadian health care facilities.

Buffy coat

A light-coloured layer of blood that contains mostly white blood cells. Buffy coat is obtained when blood is centrifuged or allowed to stand in a test tube. The red blood cells settle to the bottom and the plasma rises and the buffy coat is between them.

CISCO

Computerized Information System for Centre Operations. A blood information system specifically designed to meet the needs of Blood Services. In addition to tracking donor history information, it will support all blood centre operations including recruiting donors, scheduling clinics, etc.

Crisis management

A critical element of system safety. It is the way in which crises are dealt with and requires a management plan.

Cross-matching

Testing of blood samples from the donation and the recipient to identify immunologic compatibility.

Cryoprecipitated AHF

Antihemophilic factor (AHF) is also called factor VIII. The cryoprecipitated AHF also contains fibrinogen, von Willebrand factor and factor XIII. This product can be used to correct deficiency of these coagulation factors. Hemophilia A or factor VIII deficiency may be treated with Cryoprecipitate AHF or lyophilized factor VIII concentrate.

Data Management System (DMS)

A fully integrated computer system. In state-of-the-art blood centres the data management system would minimize clerical error in the manufacture of blood components by minimizing manual steps in data management.

de minimis risk

As close as possible to zero risk.

Directed donation

A blood donation intended for a specific recipient.

Donor screening

A process by which the blood donor clinic staff assess whether the donation of blood will be harmful to the donor and whether there is a risk of disease transmission to the recipient.

Endemic

Describes a disease that occurs widely in a particular population but has a low mortality; used in contrast to epidemic.

Factor VIII

Factor VIII is an important element for the blood clotting process. The plasma is usually obtained by plasmapheresis or from whole blood donors and prepared by pharmaceutical firms by fractionation and lyophilization of pooled plasma.

Factor IX

A concentrate used to treat patients with hemophilia B or Christmas disease, but can also be used to treat patients with congenital factor VII and factor X deficiencies. Factor IX is prepared commercially by the fractionation of pooled plasma (plasma collected from several donors).

False negative test result

A negative test result in a sample from a person who has the condition for which he or she is being screened.

False positive test result

A positive test result in a sample from a person who does not have the condition for which he or she is being screened.

Feiba

A product used by some hemophiliacs who cannot tolerate factor VIII.

Fresh-frozen plasma

Fresh-frozen plasma can be used to replace all coagulation factors, and so it is especially useful to treat multiple coagulation deficiencies occurring in patients with liver failure, DIC, vitamin K deficiency or warfarin toxicity or patients needing massive transfusion.

Glycerolization

Adding glycerol to a unit of red cells for the purpose of freezing.

Good Manufacturing Practices (GMPs)

Good Manufacturing Practices involve a comprehensive system of organization and management (administrative and supervisory) and specify many aspects of training, equipment, reagents, techniques and documentation.

Governance/ Governance function

Governance is the act of making decisions on behalf of the Canadian people. Its two sub-components are priority setting and funding, and regulation.

HBsAg

Hepatitis B Surface Antigen. The most reliable method for preventing transmission of viral hepatitis B is to screen blood donors for the presence of HBsAg.

Hematocrit

The proportion of red cells in whole blood expressed as a percentage.

Hemolytic transfusion reactions

A reaction usually due to the transfusion of ABO-incompatible blood following the improper identification of the recipient, either when the cross-match specimen is taken or when the donor blood is transfused.

Hemophilia

Hemophilia A: A hereditary disorder characterized by greatly prolonged coagulation time. The blood fails to clot and bleeding occurs, especially in males because of the inheritance of a deficiency of factor VIII.

Hemophilia B: Also called Christmas disease, which is a hemophilia-like disease caused by a lack of factor IX.

Hepatitis

An inflammatory condition of the liver often caused by viral infection.

Hepatitis B Virus

Hepatitis B virus (HBV) is a common cause of acute and chronic liver disease with worldwide distribution. The virus is transmitted by blood and other body fluids such as semen, cervical secretions and wound exudates.

Hepatitis C Virus

Hepatitis C virus (HCV), formerly non-A/non-B hepatitis, is a major cause of acute and chronic hepatitis. The majority of people who become infected with HCV will remain chronically infected and at least 50% will develop chronic hepatitis.

HTLV I and II (Human T-cell lymphotropic virus)

HTLV I and II were the first human retroviruses to be discovered. They belong to a subclass of retroviruses only distantly related to HIV. HTLV I is a virus associated with adult T-cell leukemia. HTLV II is a virus associated with hairy cell leukemia.

Immune globulin/ immunoglobulin

A plasma derivative. One of a family of closely related though not identical proteins capable of acting as antibodies.

Incidence

The rate at which a condition is being newly acquired in a population during a period of time. In the context of repeat donors, annual incidence rates are usually calculated as the number of new cases divided by the number of person-years of observation during which these conditions were acquired.

Liquid plasma

Liquid plasma was formerly known as "single donor plasma." Liquid plasma contains variable and usually small amounts of the labile coagulation factors V and VIII and thus is not recommended for treatment of patients who have a deficiency of these factors. Liquid plasma can be used for treatment of stable coagulation deficiency, especially factor IX deficiency.

Lookback

The process of identifying persons who may have received blood containing HIV. Recipients of blood or blood components are notified when previous donors are found to be infected with the virus. This process is necessary due to the exceptionally long incubation period of AIDS.

Parasite

An organism that lives within, upon or at the expense of another organism, known as the host, without contributing to the survival of the host.

Plasma derivatives

The liquid portion of whole blood containing water, electrolytes, glucose, fats, proteins and gases. Plasma contains all the clotting factors necessary for coagulation, but in an inactive form. Once coagulation occurs, the fluid is converted to serum.

Plasmapheresis

A procedure whereby the plasma is separated from the cellular components in a collection bag and retained, and then the cells are reinfused to the donor. Plasmapheresis may be used to increase the inventory of fresh-frozen plasma of a particular ABO group, such as group AB. The procedure may be used to collect immune plasma for patients who are immunosuppressed and have been exposed to varicella or herpes.

Plateletpheresis

A procedure whereby platelets are selectively separated from the whole blood and retained in a collection bag while the remaining components are reinfused to the donor.

Potency

The strength of a particular drug, toxin or hazard. When blood components lack

potency, for example, when there are a suboptimal number of platelets per unit, recipients may have adverse reactions, such as bleeding or anemia.

Prenatal testing

Testing for disease while an infant is in utero.

Prevalence

The proportion of a population with a given condition. When estimating prevalence, it is irrelevant whether the condition is newly acquired or long-standing.

Process management

Management of the process that extends from obtaining blood from donors to the manufacture of the product.

Product assurance

A means of assuring that products meet customer requirements and verifying that the manufacturing process is compliant.

Quality Control

Quality Control (QC) consists of a set of procedures undertaken by blood centre staff for the continued evaluation of the quality of work. QC is the minimum type of quality program involving inspection and testing of the product. There is limited provision for feedback to design/planning.

Quality programs

Quality programs begin as process controls for operations but extend into the higher functional levels of the system. They help in forming goals, such as error-free processing and, therefore, also dominate the planning and design function.

Risk assessment

The qualitative or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards or from the absence of beneficial influences.

Risk management

The steps taken to reduce the levels of risk to which an individual or a population is subject. The steps can involve the introduction or removal of controls to reduce risks.

Risk perception

There is often a difference between the measurement of a risk and the public's perception of that risk.

Standard Operating Procedures (SOPs)

Clearly written instructions authorized by the CRCS National Office, delineating every routine activity carried out during the blood transfusion process.

TD Markers

Transmissible disease markers. Used to describe the antigen or antibody used in screening tests as an indication of whether a blood sample contains an infectious disease agent.

Washed red cells

Patients who have febrile or allergic transfusion reaction to ordinary units of red cells may benefit from receiving washed red blood cells. The washing process removes leukocytes, the cause of most febrile reactions, and plasma, the cause of most allergic reactions. Washed red blood cells are used for the rare patient with IgA deficiency and anti-IgA.

Window Period

The length of time it takes after being infected for detectable antibodies to form. The length depends upon the particular infection and the technology that is used in the test.

TERMS OF REFERENCE

Recommendations to the Commissioner from G.E. Connell, Principal Adviser,
Regarding the Interim Report on Safety of the Blood System
February 3, 1994

The Commissioner is required to file an interim report "on the safety of the blood system, with appropriate recommendations on actions which might be taken to address any current shortcomings".

Aspects of safety, broadly defined, in the blood system, might be classified under the following sectors or activities - (i) governance (ii) regulation (iii) management (iv) operations and (v) clinical service delivery. The following commentary illustrates the nature of issues which might be addressed at each of these levels.

(i) Governance

The government of Canada and the governments of the provinces and territories are ultimately responsible for ensuring that the relevant departments and agencies have clearly defined responsibilities, and that management and operations throughout the system are conducted with due diligence, conforming to accepted standards of safety. Where responsibilities are delegated to, or assumed by, corporations such as the Canadian Blood Agency or the Canadian Red Cross Society, the governing boards of those organizations are responsible for safety in all matters within their respective mandates. Delegation does not, however, diminish the accountability borne by governments.

(ii) Regulation

Regulation is a special responsibility within the overall accountability of governments. The responsibility for regulation is normally defined in a statute such as the Food and Drugs Act (R.S.C. 1985, c.F-27). The regulations under that statute assign the regulatory function and powers of the federal government to a designated agency, the Health Protection Branch of Health and Welfare Canada. The Bureau of Biologics of the Health Protection Branch has specific responsibility for safety of all processes in, and products of the blood system in Canada, as well as for the safety of all blood products imported into Canada. The main regulatory issues relevant to the Interim Report are whether the regulations are appropriate for the standards of safety that are desirable, and whether the regulations are being adequately and efficiently enforced.

(iii) Management

The safety of any enterprise depends upon the quality of management. Each manager at his/her level of responsibility must have a good understanding of the principles and practice of risk management. This requires first of all

awareness of the potential risks that are inherent in the processes, and those that might be introduced by the forces of nature and other external agencies or events. Secondly, good management requires careful planning and design of processes and products to ensure that they are as resistant as possible to known and unknown risks. There must be backup systems, contingency plans, and various forms of insurance which would come into play in the event of a system failure.

(iv) Operations

The primary safety consideration in any routine process is that there be standard operating procedures for production, analysis, record-keeping and reporting which conform to high standards. Standards for equipment and materials must also be defined and observed. Staff must be well-trained and tested periodically. Processes and products must be monitored according to a pattern which will give early warning of problems.

The screening of donors is a specially critical element at the operational level in the blood system. The review should ensure that the objectives and procedures in screening are clear, and that satisfactory outcomes are achieved.

(v) Clinical Service Delivery

The "blood system", broadly defined, might well be taken to include all aspects of therapeutic use of blood products and related services. The broad definition would, therefore, bring under review by the Commission institutional management of products and services by hospitals, and individual care by health care professionals, with regard to both safety and efficacy.

Evidence that infectious diseases, especially AIDS, have been transmitted through therapeutic use of blood and blood products is the most important of the considerations which led to the appointment of the Commission, and the requirement for an interim report. This must, therefore, be the major consideration in formulating a plan for preparation of that report.

There is an emerging international consensus as to the "good management practices" which are likely to minimize the risk of propagation of infectious disease through blood products. It would be possible, therefore, to compare Canadian standards and procedures with the highest international standards and procedures by means of a professional peer audit. This audit could be conducted by specialists in the appropriate disciplines and supervised by a management committee consisting of leaders in their respective fields. This approach is applicable in particular to management and operations of the Canadian Red Cross Society, and to the regulatory work of the Bureau of Biologics.

It will be necessary to exclude from the Interim Report safety considerations in the domain of

clinical service delivery in the hospitals. There are simply too many institutions, specialties and clinical conditions, and too much diversity in standards of practice. A comprehensive peer review of safety which met the high standards expected of the Commissioner would make unreasonable demands both in time and money. It should be possible to gain some insight into safety issues at the clinical level at a later stage of the work of the Commission, but this prospect should not be permitted to delay the Interim Report.

A comparative peer review audit would not be readily applicable to the complex process of policy formation and direction at various levels of government. Such matters clearly come within the terms of reference of the Commissioner but probably need not be addressed as part of the Interim Report. If there were deemed to be problems arising out of the structure or style of governments, they would not be likely to be of a character such that remedies could be designed and applied on a very short time scale. It is to be expected in the course of public hearings of the Inquiry that evidence from a number of witnesses will have some bearing upon the roles of the respective governments and the impact of their policies and administration upon the overall quality of the blood system, including safety considerations. This might well prove to be the most effective way to initiate consideration of these matters.

The Canadian Blood Agency, which serves as the agent of the provincial and territorial governments in their interactions with the blood system, obviously has critical importance in matters of safety. The CBA is not, however, an entity to which a comparative expert review could readily be applied. There are no exact parallels to the CBA in other jurisdictions, nor are there accepted standards or guidelines against which its performance could be reviewed. As with governments themselves the safety issues, though of fundamental importance are likely to be manifested as an aspect of broader policies and operational relationships. The safety issues are not likely to be susceptible to the highly focused diagnosis and remedy that one would expect from a peer review. As with governments the Inquiry can expect to hear from a number of witnesses evidence which bears upon the role of the CBA in safety. This may well prove to be the most important source of illumination for the final report.

The interim review should, however, be designed in a manner which will allow the capture of information and insight which might prove to be highly relevant to the role and efficacy of the CBA in matters of safety. The recommendations set out below have been framed with this objective in mind.

These considerations lead to the following recommendations:

Recommendation 1: The scope of the Interim Report should be limited to matters of safety in the Blood Program of the Canadian Red Cross Society and the work of the regulatory arm of the federal government, the Bureau of Biologics. It may prove to be feasible to formulate some conclusions relevant to the role of the Canadian Blood Agency with regard to safety.

Recommendation 2: Special attention should be given in the review to operational and regulatory procedures which are relevant to the risk of transmission of infectious diseases through therapeutic use of blood and blood products.

This recommendation should be taken to include the issue of contingency plans for dealing with emergencies and system failures.

Recommendation 3: The review should be based both on examination of documents and site inspection conducted by expert teams.

The documents to be reviewed should include all relevant regulations, managerial protocols, standard operating procedures and reports.

Recommendation 4: The expert review should include comparison of the Canadian system with those of the United States, the United Kingdom, Australia and New Zealand.

These nations are recommended as the standards for comparison because they are judged by the World Health organization to have blood systems of the highest quality, and because the relevant documents are readily accessible.

Recommendation 5: Site visits by experts should be made to the central offices of the Bureau of Biologics and the Red Cross, and to some or all of the Regional Centres of the Red Cross.

The number of Regional Centres to be visited should be determined by the Management Committee (see below) in the light of experience in the initial visits. One of the complicating factors is that the Red Cross will shortly initiate a major change in operating procedures at the Regional Centres. The changes are likely to be completed within a few months. It would probably not be feasible, however, to defer all site visits until the conversion is complete. There might well be good value in ensuring that at least one or two of the proposed visits took place before conversion was launched. The details of the approach to be taken should be left to the judgment of the Management Committee.

The site inspections will be conducted by teams of three to five individuals who have, collectively, the expertise required for the assigned task. Each site might require the presence of the team for as much as four to five days. Several different teams of visitors may have to be recruited to complete the entire review. The teams should receive comprehensive and consistent briefings in advance of their visits. At the conclusion of the site visits the findings of the teams will have to be brought together in a consolidated Report to the Commissioner.

Recommendation 7: The work of review teams should be supervised by a Management Committee, which should also take responsibility for directing the preparation of a

report to the Commissioner on the safety of the system.

Recommendation 8: The Management Committee should be made up of individuals who are leading authorities and who have, collectively, expertise in the following fields: regulation, blood centre management, quality assurance, data systems management, risk management, microbiology and infectious diseases.

Recommendation 9: The Canadian Blood Agency should be invited to submit a brief for review by the Management Committee.

This brief should provide an account of the issues, the policies and the actions of the Agency which have relevance to the safety of the system. The Management Committee would be asked to review this brief and to take any action to follow up which it judges to be within its mandate.

Recommendation 10: The Report of the Management Committee should be released to parties, and comments received, before action is taken by the Commissioner. The Interim Report on Safety of the Blood System should be based on the Report of the Management Committee, on information and views presented by the parties, and on such other sources that the Commissioner believes to be relevant.

APPENDIX II

The review of the Edmonton Centre was conducted by Jenni Lee Robins, Dr. Harvey Skinner, Dr. Stanley Read and Dr. John Shortreed on May 25-27, 1994.

EDMONTON RED CROSS BLOOD TRANSFUSION CENTRE

Methodology:

Team used the Critical Control Points in the Quality Program System (attached) as general discussion outline. We used selected sections of the Canadian Red Cross Society 1992 Centre Quality System Assessment Checklist to discuss more specific system issues.

Process:

Team met with all managers of major functions including the Quality Assessment specialist and discussed Critical Control Points. This forum provided us with an opportunity to understand how Critical Control Points had been implemented within each major system. We did not discuss each point, but selected specific points. Attached is a list of the documentation provided to demonstrate progress in implementing Quality Programs.

Additionally, team visited the donor area and the laboratory.

Additional Information:

Edmonton is one of the pilot centres within CRCS using the new SOPs. Also, Edmonton is the pilot centre for implementation of CISCO. CISCO review will be documented separately.

Conclusions:

The staff is extremely helpful. They are motivated and enthusiastic in discussing the implementation of cGMPs and process improvement. Although somewhat overwhelmed with all that needs to be accomplished, they are determined to move forward because they believe it is the appropriate business strategy.

As indicated in the attached list of documents, the Edmonton Centre has made significant progress in implementing cGMPs.

Although centre staff recognized the work done at Red Cross headquarters had involved centre staff input, the Edmonton staff were in the process of suggesting change in specific outputs. For example: SOPs were too detailed and should be used as training manuals. This indicates the process of continuous improvement has been embraced by CRCS.

Overall, team was impressed with the Edmonton staff.

Documentation in Support of Quality Program System Implementation:

- A. Organizational Charts
Blood Services Regulatory Environment
- B. Performance Evaluation Form and Training Profile
Personnel Protection Equipment
- D. Quality System Assessment: Supplier Defective Collection Pack Summary
Procedure for Acceptance of Test Kits Labs for TTD
Evaluation and Approval of Equipment/Supplies
Reporting of Defective Equipment/Supplies
Supplier Selection and Evaluation by Blood Services
- F. Approval Process for SOP Variance/Change Request
- H. 1994 Activity Report - Incident Management
Internal Incident Management Form
Donor Incidents
Computer Incidents
Defective Equipment/Supplies
Blood Component Lab Incident
- I. Centre Inspection Report
Centre Inspection Policies
1993-94 License Forms
- J. Canadian Red Cross Society Core Business Process

Opportunities for Improvement:

Historical process of prelabeling of units with prior ABO group should be discontinued.

Historical practice applying collection date versus expiration date should be discontinued.

Interface between laboratory devices and labelling applications should be explored as soon as possible, to eliminate manual reconciliation process.

Process for capturing donor registration form error could be merged with incident reporting systems to ensure appropriate follow up on corrective action.

VANCOUVER RED CROSS BLOOD TRANSFUSION CENTRE

The review of the Vancouver Blood Centre was conducted by Jude Tessel, Tom Zuck & Martin Schechter on June 29-30, 1994.

The team found the Vancouver Blood Centre essentially in control as managed and run by dedicated and knowledgeable staff. The team feels the safety of the blood it supplies is being carefully guarded under its current operations. It is clear that the entire Canadian blood system is undergoing dramatic and rapid change from a medical service culture to a pharmaceutical manufacturing culture. It is clear that the staff is experiencing significant stress and anxiety as they cope with rapid and profound change. It appears that the Centre management is delaying some process improvements pending guidance and/or SOP's from National. This strategy may be somewhat more passive than may be desirable.

The lack of a coherent data management system poses the single greatest threat to the prevention of the release of an unsuitable unit for transfusion by the Vancouver Centre. Such vital processes such as duplicate record checking, labelling, and product release procedures can only be controlled with computerized data management methods. It is beyond the power of centre staff to correct this deficiency; action and process implementation by National is controlling.

However, certain management improvements could be instituted that would improve the systems that protect the Centre from the release of blood components unsuitable for transfusion.

- review of SOP's currently used in production; they have not been reviewed in over two years - this review could be performed independently, or at least concomitantly, with efforts to institute new National SOP's
- develop process change control protocols to assure changes are orderly and documented within the Centre
- validation protocols should be developed for both new and established manufacturing equipment, procedures, and methods
- certain labelling practices, such as prelabeling in the clinic with prior ABO group and affixing only the drawing date rather than expiration date by the Centre, could be modified with minimal effort and disruption.
- protocols to manage error and accidents systematically could be developed locally
- initiate efforts to change a system dependent on the quality and performance of superior personnel to a system that depends on process controls that are not dependent on perfect performance of people.

HALIFAX RED CROSS BLOOD TRANSFUSION CENTRE

A site team consisting of Jenni Lee Robins and Dr. Harvey Skinner visited the Halifax Centre on August 4-5, 1994.

Methodology:

Team used the Critical Control Points in the Quality Program System as general discussion outline. We used selected sections of the Canadian Red Cross Society 1992 Centre Quality System Assessment Checklist to discuss more specific system issues.

Process:

Team met with all managers of major functions including the Quality Assessment specialist and discussed Critical Control Points. This forum provided us with an opportunity to understand how Critical Control Points had been implemented within each major system. We did not discuss each point, but selected specific points. Attached is a list of the documentation provided to demonstrate progress in implementing Quality Programs.

Conclusions:

The staff is extremely helpful. They are motivated and enthusiastic in discussing the implementation of cGMPs and process improvement. Although somewhat overwhelmed with all that needs to be accomplished, they are determined to move forward because they believe it is the appropriate business strategy.

Team was impressed with the Halifax staff.

Opportunities for Improvement:

Historical process of prelabeling of units with prior ABO group should be discontinued. ASAP.

Historical practice applying collection date versus expiration date should be discontinued.

Interface between laboratory devices and labelling applications should be explored as soon as possible, to eliminate manual reconciliation process.

Process for capturing donor registration form error could be merged with incident reporting systems to ensure appropriate follow up on corrective action.

Tools to manage Error Review Process should be developed so that emphasis can be on root cause analysis and trend monitoring versus "quick-fixes."

Documentation in Support of Quality Program System Implementation:

- A. Organizational Charts
Blood Services Regulatory Environment
- B. Performance Evaluation Form and Training Profile
Personnel Protection Equipment
- D. Quality System Assessment: Supplier Defective Collection Pack Summary
Procedure for Acceptance of Test Kits Labs for TTD
Evaluation and Approval of Equipment/Supplies
Reporting of Defective Equipment/Supplies
Supplier Selection and Evaluation by Blood Services
- F. Approval Process for SOP Variance/Change Request
- H. 1994 Activity Report - Incident Management
Internal Incident Management Form
Donor Incidents
Computer Incidents
Defective Equipment/Supplies
Blood Component Lab Incident
- I. Centre Inspection Report
Centre Inspection Policies
1993-94 License Forms
- J. Canadian Red Cross Society Core Business Process

SYSTEM BEING ASSESSED: SYSTEM A: QUALITY PROGRAM

Critical Control Point: L Internal Assessment
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Key Elements:

1. Written procedures to conduct ongoing internal assessments by knowledgeable operations staff not directly responsible for performing procedures being audited.
2. Written procedures to conduct periodic internal assessments by knowledgeable quality unit personnel.
3. Report of results of internal assessment reported to management in writing and reviewed by responsible head.
4. Corrective action facilitated/monitored by quality unit.
5. Internal assessments address systems and processes by evaluating key elements and critical control points.
6. Process exists to periodically assess each critical system including:

<ul style="list-style-type: none"> ➤ A. Quality Program ➤ B. Donor Suitability ➤ C. Blood Collection ➤ D. Component Processing ➤ E. Testing 	<ul style="list-style-type: none"> ➤ F. Review and Labeling ➤ G. Storage and Distribution ➤ I. Compatibility Testing ➤ J. Blood Administration ➤ K. Investigation of Adverse Effects ➤ M. Information Management
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7. Assessment of the following processes within each major system:
 - Organizational Issues
 - Personnel Selection/Training/Education
 - Validation/Calibration/Preventive Maintenance/Proficiency Testing
 - Supplier Qualification
 - Process Control
 - Documentation/Record-Keeping/Record Review
 - Label Control
 - Incident/Error/Accident Review
 - Internal Assessment
 - Process Improvement

SYSTEM BEING ASSESSED: SYSTEM A: QUALITY PROGRAM

Critical Control Point: J. Process Improvement

Key Elements:

1. Infrastructure and procedure to facilitate process improvement/problem-solving.
2. Process improvement procedure will include:
 - a. Verification/definition of problem.
 - b. Collection of baseline data, patterns, influential factors.
 - c. List of possible solutions for improvement.
 - d. Selection of solution.
 - e. Development of implementation plan.
 - f. Commitment from organization to support plan.
 - g. Execution plan, including indicators to identify system drift.
 - h. Indicators to monitor impact of plan.
3. Training of staff in use of problem-solving methods and tools.
4. Appropriate use of problem-solving process.
5. Availability of resources to conduct problem-solving meetings.
6. Capture of cost of nonconformance.

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Report on the Site Visit - August 24, 1994
CRC National Testing Laboratory
Prepared by: Carol Major - Site Team Member

Introduction:

The purpose of the visit to the National Testing Laboratory (NTL) was to determine with respect to Transmissible Diseases:

How decisions are made regarding which tests will be carried out on the blood supply.

How individual products are selected for use.

Type and scope of quality assurance programs in place for laboratory testing.

Algorithms for confirmatory testing.

Format:

The Commission Site Team consisted of Dr. Penny Chan, Dr. Stan Read and Carol Major. CRC staff (Dr. Peter Gill, Dr. Tom Walker, Vito Scalia, Sam Schwisberg (counsel) and Shelley Brice) met with the team and discussed in detail many aspects of the above areas of interest during the morning. In the afternoon, the team toured the entire NTL, but focused on the Transmissible Diseases Laboratory and examined entering, testing and reporting of specimens. A wrap up session was held with the CRC staff before ending the visit at about 4:30 pm.

Observations:

Dr. Peter Gill, Director of NTL provided an overview of NTL using a series of overheads which had been prepared for a previous site visit by the Commission. These slides are attached in appendix A. The organizational chart of NTL shows 5 main subsections: **Molecular Virology** which is investigating hepatitis C, HIV and HTLV recombinant proteins using a baculovirus vector system, **Testing Support** which is responsible for all CRC Centre QC tabulation and technical support, **Immunocytometry** which is investigating cell markers and their implication in diagnosis of various conditions and diseases, **Plasmapheresis** and **IgA** responsible for plasmapheresis donor welfare, and the **Transmissible Disease Laboratory (TDL)** which together with Testing Support, is responsible for all of the areas of interest for the site visit.

Organization of the TDL:

Vito Scalia is the manager of the TDL. Two charge Technologists report to Vito, and seven laboratory Technologists and one lab helper report to the technologists. The lab is responsible for confirmatory testing for all viral markers (i.e. all repeat reactive specimens forwarded by CRC centres for hepatitis B and C, HTLV-1, and HIV), the evaluation and validation of all products and accompanying software and instrumentation, the implementation of all tests, equipment and software in CRC centres, technical support for CRC centres, the development of national SOP's (regarding laboratory testing), and the quality control program. In addition, the TDL plays a role in the investigation of alleged transfusion transmitted infections and participates in national and international collaborations.

Decisions regarding infectious diseases screening:

Hepatitis B surface antigen screening has been in place for all donations since 1972. HIV 1 testing commenced in 1985, HTLV 1 and hepatitis C screening began in May of 1990. Confirmatory testing for these agents is carried out by NTL. Syphilis screening has been carried out since the beginning of blood banking in Canada, and all confirmatory testing for syphilis is done in the Public Health Laboratory Systems of respective provinces. In addition, centres screen for cytomegalo virus antibody to identify a sufficient number of CMV negative units to meet local demands. No confirmatory testing is carried out for CMV. NTL does not get involved in product selection or purchase for CMV. Therefore, a number of different methods/products are in use for CMV antibody screening.

The process of determining which agents will be screened is complex. The Bureau of Biologics has the ability to require the CRC to test for specific agents, however, this does not happen. The NTL is generally aware of tests becoming available to test for blood borne pathogens and initiates discussion to either evaluate the risk of the agent in the Canadian blood donor population (eg HTLV 1), or to evaluate the tests with a view to immediate implementation of a new test (eg hepatitis C). Funds to support new tests were authorized by the Canadian Blood Committee, now the Canadian Blood Agency.

Decisions regarding purchase of products:

Kits to be considered for use for screening by the CRC, must be FDA approved and have Center for Biologics Evaluation and Research (CBER) master lot release. Both of these requirements are US based. In addition, the HIV products must have Notice of Compliance, from the Health Protection Branch, Bureau of Medical Devices, Health Canada. (Canada does not have a process of authorization of test kits for agents other than HIV). The Bureau of Biologics must approve all tests selected by the CRC.

Staff of the NTL investigate qualified products by examining the package insert data, determining availability, assessing field experience of other users, and determining the manufacturer's interest in a CRC contract through meetings and presentations. From this

information, a short list of manufacturers is prepared and a committee struck to develop a Request for Proposal. For the current contract, agreement was reached by senior management that all products for HIV, hepatitis B, and HTLV should be purchased from a single supplier in order to facilitate technical support, efficiency, and cost effectiveness. This decision limited the RFP to two applicants - Abbott and Sanofi. While it is convenient and practical to deal with only one company, it severely limits the selection of products. Indeed, it is extremely unlikely that the best products will be available from a single manufacturer for all markers, and therefore some compromise is likely to occur.

The RFP was not examined by the team, but it includes details such as: consistent highest possible quality test performance - including replacing an existing product with a newer, better version should one become available during the contract period; practicality and ease of use, manufacturer's provision of technical support and training, assistance and ease of integration into laboratory systems, equipment and software packages. The supplier presents their proposal to the selection committee and it is reviewed against a complex decision matrix. Values are assigned to each assessment criteria and following modest evaluation of the products and a visit to audit the manufacturing site, a recommendation to purchase is made by the selection committee.

Whenever a new product is selected, a detailed evaluation/validation is carried out in collaboration with one or more centres and presented to the Bureau of Biologics for approval before implementation can take place.

Product Evaluation:

Preselection Evaluation: Products for which an RFP have been received are evaluated by the NTL. For all products, three different lots provided by the manufacturer are assessed for sensitivity as follows: for HIV1/2, 100 CRC stored positive samples and 3 seroconversion panels purchased from BBI are used; for HTLV, 100 stored positives and one BBI seroconversion panel are tested; for HBsAg, the Paul Erlich 0.3 ng standard is diluted and tested. Specificity and product stability is not assessed during this phase of the process, but information from the package insert and provided by the manufacturers is taken into consideration. Reproducibility is assessed using 30 replicates of a diluted positive specimen (low reactive) on 5 plates from each of 3 lots provided by the manufacturer. It is not possible to accurately estimate sensitivity of any of the products based on the evaluations performed in-house. The methods chosen do allow some comparison between products, assuming that all products are tested with the same panel, and that the seroconversion panel are not chosen to be biased in favour of a specific manufacturer.

Decision Matrix:

The decision matrix assigns the relative value to each characteristic of each test. It includes sections on performance (sensitivity, specificity, reproducibility, stability), equipment, technical service and support, scientific support, manufacturer's experience. It is difficult to

rationalize the relative weightings applied to various characteristics. For example, of a possible 340 points observed sensitivity is worth 10 points, manufacturer's stated sensitivity is worth 7 points and the amount of space required for the equipment is worth 42 (6 pieces X 7 points each). Performance characteristics must be more highly valued than the amount of space occupied by the equipment. CRC has previously operated using at least two testing systems requiring different equipment, space should not be a criteria worth more than the ability of the test to detect positive specimens. Rather than using manufacturer's stated sensitivity and specificity, a serious investigation of current product field performance should be undertaken. Product insert information is data collected for FDA approval. It is collected under ideal circumstances, and may not reflect the true operating characteristics of the current product.

Another concern regarding the decision matrix is the presence of on site performance values for specificity and stability although neither of these characteristics are evaluated by NTL during the preselection phase.

Post-selection Evaluation:

Whenever a new product is selected, parallel testing of a minimum of 10,000 donations must be carried out in at least two CRC centres, in order to satisfy Bureau of Biologics requirements. The centres provide written reports regarding kit performance and operational considerations. At this point the decision to purchase a product has already been made by CRC officials. If information from this full scale evaluation of the product refutes information gathered earlier (i.e. specificity), it should be possible to review the decision to purchase. To date BoB has never denied use of a recommended product, although contract performance on a number of markers was significantly under manufacturer's claims.

Other notes regarding current contract:

The product evaluated for HTLV testing was not intended to be used for HTLV testing. Another Sanofi product which did not have FDA approval at the time, although it was anticipated shortly was to be the kit provided under the terms of the contract. The Sanofi product did not receive FDA approval and therefore could not be implemented. The evaluated FDA approved product was brought in by the supplier as a substitute and was accepted by the CRC. Subsequently, the product was rejected by the CRC and yet another supplier found to substitute for the kit originally accepted.

Quality Assurance Programs:

The QA process begins prior to implementation of a product. All aspects of the software and equipment are examined thoroughly by the NTL and by CRC centres. Guidelines and verification guides are developed by the vendor in collaboration with NTL. Centralized and/or on-site training is provided by the vendor in collaboration with NTL. Staff must exhibit proficiency with new methods. Each set of equipment and software are validated at

each site before the new test is implemented.

A sophisticated system of kit lot release, monitoring testing data, use of test panels, responding to support requests on a 24 hour basis, equipment/assay troubleshooting, and liaising with vendors form the basis of the QC/QA functions carried out by NTL staff. Manufacturers provide data to the NTL regarding performance of each kit lot in the CBER panel (8 members) and the NTL panel (4 members). Following NTL acceptance, the NTL in-house panel is tested with the lot by NTL. NTL can accept, conditionally accept or reject a kit lot, although, it seems that the criteria for rejection are fairly difficult to meet. Once received in the field, each centre tests new kits with an NTL panel. If satisfactory, the lot is implemented, but subject to continuous monitoring. If problems occur and NTL can demonstrate significant deterioration or performance outside of contractual agreement, the kit lot will be removed and replaced by the manufacturer.

External Proficiency Programs:

NTL participates in CAP, LCDC, and CDC proficiency testing programs. They are currently arranging to participate in the Ontario LPTP. Centres participate in the CAP programs and provincial programs where available (Ontario - LPTP). Recently a proficiency panel identified a problem of carry over in hepatitis B testing.

Confirmatory Testing:

Confirmatory testing for hepatitis B, hepatitis C, HTLV 1 and HIV 1/2 is carried out at the NTL. Donor re-entry is not permitted under any circumstances, so results generated from confirmatory testing are used to supplement information provided to the donor on his/her deferral letter. The decisions regarding confirmatory algorithms are therefore made by NTL using the best available information on techniques. Where possible, FDA approved methods/kits are used, but frequently additional non-approved or research procedures are used in confirmatory algorithms.

HIV 1/2:

HIV2 EIA is run on all repeatedly reactive HIV1/2 specimens. HIV1 (Dupont - FDA approved) (and HIV2 (Cambridge - not approved) if required) western blot is performed. Another HIV1/2 (Biochem Pharma, Detect HIV (not approved)) is also run on all specimens. Results are reported as positive, negative or indeterminate using a combination of WHO and package insert criteria. HIV p24 antigen testing is not done.

HTLV confirmatory testing is done using the Diagnostic Biotechnology HTLV 3.2 blot (not approved) which has unique recombinant gp46 bands from HTLV1 and HTLV2. In addition the Roche HTLV PCR (investigational use) kit is under evaluation. Specimens are reported as positive, negative or indeterminate. Attempts are made based on the DB blot to distinguish HTLV1 and HTLV2. PCR is currently under investigation as a supplemental test for HTLV1 and 2 discrimination.

Problem specimens from HTLV and HIV testing are referred to LCDC when NTL is asked to perform follow up and/or consultation in indeterminate cases.

HBsAg positive specimens are confirmed by neutralization (FDA approved).

Hepatitis C specimens are confirmed using RIBA (not FDA approved). Two bands are required for positivity and specimens are reported as positive, negative or indeterminate.

Other testing carried out at NTL includes: anti HBs (Abbott - RIA), anti HBcore (Ortho) for the investigation of transfusion related infections.

Laboratory Observations:

General: The laboratory was spacious, well equipped and very well maintained. Records were in meticulous order. The laboratory was very adequately staffed and equipped for the workload carried out.

Specimen tracking: Specimens referred to NTL are shipped via courier with an intake sheet providing details of testing in the centre. The sample is identified by the unit number. On receipt at NTL a new number is assigned which is handwritten in sequential order or colour coded (corresponding to the tests required) 5 or 10 mm dot. Dots with the same number are affixed to the top of the tube, the side of the tube and the intake sheet. The original unit number remains on the tube.

Procedures: Equipment was observed, but laboratory activity was minimal as it was near the end of the working day.

Results and Records: Final results were observed for HIV 1 and 2, and HTLV western blots, as well as, hep C RIBA results. A large proportion of all tests are indeterminate (35-69%). Reports on intake sheet were examined, and were found to be in good order - results duly recorded and verified by appropriate staff.

Other observations/information from site visit:

- 13 cases of HIV infection related to blood transfusions have been confirmed since testing for HIV began in 1985. Investigation of these cases has identified: 1 case - where although Abbott was negative in 1986, the 1986 specimen was positive when retested with Dupont in 1988; 1 case of negative screening in 1988 which is still negative with available techniques, although the donor has seroconverted; and one case of human error where the unit tested positive but was accidentally put back into the clean pool of units.
- specimens from units are not kept unless they are sent to NTL for confirmation.
- NTL keeps all specimens received indefinitely.
- investigation of alleged cases does not routinely include the retrieving of test information specific to the unit(s) in question
- lookback/traceback procedures are of limited value as donor records were not necessarily kept.
- the information provided by the Centre medical director regarding confirmatory testing to the donor or donor's physician is at the discretion of the medical director.
- NTL staff are wary of manufacturers with respect to their integrity regarding admission of product or equipment related problems. This was expressed as frustration in the extent of

NTL demonstration of specific problems required before action was taken, ie specificity problems with HTLV, washer related problems with all products, specificity problems related to individual lot numbers, or awareness of potential for problems based on increasing negative specimen/control mean values etc.

- in spite of lack of trust regarding support related aspects of the contract, CRC seems to have complete faith in manufacturers to report accurate performance data on products before selection. ie validation of sensitivity and specificity claims is not adequately carried out.
- since the implementation of the current contract with Sanofi, repeat reactive rates have increased and there have been significant increases in the proportion of indeterminate results generated for hep B, and HIV.
- indeterminates are also problematic for hep C (36%) and HTLV (69%)
- the increase of repeat reactive rates has led to the permanent deferral of more than 6000 additional donors.

Comments, Discussion and Recommendations:

Product Evaluation:

There is a need to attempt to get an accurate and unbiased perspective of product performance before preparing the RFP and selecting the product.

The safety of the blood supply depends primarily on the sensitivity of the tests used in screening. While FDA and HPB approvals provide a level of confidence in products, there still exists differences in specific criteria. Data from the manufacturers should not be accepted *de facto*. All products meeting basic criteria should be evaluated for sensitivity, specificity, positive predictive value, negative predictive value, practicability, instrumentation etc. Criteria should be ranked and balanced, and evaluation must be appropriate and scientifically sound. ie at least 300 positive specimens from Canadian sources should be tested, plus as many seroconversions and window stage specimens, and strain variants as can be obtained from diagnostic testing labs. At least 5000 fresh blood donor specimens should be used to assess specificity.

Only if all performance criteria are deemed to be superior for each marker, should consideration be given to obtaining all markers from the same vendor.

On the other hand, if performance criteria for different vendors for an individual marker are deemed equal, consideration should be given to having two products in the system in order to maintain a back up should one product present problems.

Products that do not meet the entry criteria, should not be evaluated (ie do not yet have FDA approval). The situation with HTLV would not have occurred if CRC had seriously considered the product they ultimately ended up using. In fact, Sanofi might not have been eligible for the contract, if CRC had used FDA approval as a strict entry criteria.

Lot Approval:

There should be tighter control by NTL in lot approval. More extensive testing of fresh donor specimens and comparison of the mean signal/cutoff(S/C) value of those specimens to the mean value obtained on satisfactory lots. NTL should be able to specify the degree of variation acceptable. Sensitivity testing should be carried out on each lot using at least some early seroconversion specimens (real specimens as opposed to diluted specimens).

From a broader perspective - perhaps consideration should be given to the Bureau of Biologics of HPB performing the evaluation and/or lot release processes for the CRC and indeed for the diagnostic testing labs in Canada.

Appendix B contains a detailed description of the evaluation process used by the National Reference Laboratory in Australia. This lab serves as the national reference and quality assurance lab for the Australian Red Cross Centres, as well as, all the diagnostic labs in the country. HIV, HTLV and hepatitis B and C products are approved for use and manufacturers are required to maintain the standard set during the evaluation. A quality assurance program monitors every batch of every product in use in Australia (samples in Appendix C). When products fail to perform, the manufacturer must replace them. It is interesting to note that the Genetic Systems HIV1/2 kit did not meet the standards for HIV1/2 screening when evaluated in Australia. Performance differences can be observed in Appendix D.

Confirmatory Testing:

A new method of identifying incoming specimens must be found. Current methods are inherently error prone.

HIV p24 antigen testing should be incorporated into the testing algorithm. It is possible with current technologies to detect EIA positive, Western blot negative specimens which are antigen positive and in the window stage. These are important cases to document and to use for future evaluations.

The large number of indeterminate results generated for hep B, C and HTLV is disturbing. Presumably these individuals are referred to the Public Health Laboratory System of their respective province for follow up. Under the circumstances, the cost of establishing the indeterminate result should be weighed against the anxiety of receiving such a result. Some attempt should be made to determine the outcome for existing indeterminate donors. From Ontario experience, the majority of HTLV indeterminates are negative with the PHL screening test (which is different from CRC screening test) and are reported as HTLV negative. It might be more effective and anxiety relieving to skip the confirmatory test at NTL and simply report them as screen test reactive - this does not mean that you have the disease, but see your doctor for further testing. Or, use other screen tests at NTL and if negative inform the donor they have nonspecific reaction in the CRC screen test and can no longer donate.

This would not be a recommended way to proceed for HIV - in fact further attempts to resolve indeterminates should be made - ie supplemental EIA, HIV antigen and PCR - If whole blood available, it should be sent with the original specimen.

Other Testing:

CMV testing should be standardized and taken under control of NTL for evaluation, purchasing, development of SOP's, and QA programs.

Other Issues

During investigation of alleged cases of transfusion related infections, all unit records regarding testing carried out in the centre, should be carefully examined by NTL staff for test results (ie evidence of a specimen missed, or gray zone result, controls and standard values). This apparently, does not occur routinely in investigation.

Executive Summary of Recommendations

1. There must not be a requirement to purchase all tests from a single supplier. This procedure undoubtedly leads to compromise of test performance.
2. Comprehensive and scientifically valid evaluations of all aspects of kit performance must be carried out before purchasing decisions are made. Products must be equal in performance characteristics before decisions are based on operational criteria.
3. NTL must have control over setting acceptable in field performance characteristics and develop a more extensive method for kit lot approval and tighter criteria for monitoring kit lot deterioration.

APPENDIX IV

BUREAU OF BIOLOGICS REVIEW

The following report was written following a three day visit, July 25 - 27 1994 to the Bureau of Biologics in Ottawa, by Dr. John D. Cash, National Medical and Scientific Director of the Scottish National Blood Transfusion Service.

ACKNOWLEDGEMENTS

The author wishes to record his thanks to those who contributed to this investigation: notably George Connell, Penny Chan, Daryl Krepps, Douglas Kennedy and Dan Michols. All displayed much kindness and courtesy and were readily prepared to respond constructively to all questions asked.

SOME LIMITATIONS OF VISIT

Mindful that the most relevant legislation was introduced in 1989, it was unfortunate that an opportunity was not available to speak to some key former BoB players, particularly the previous long-serving Head of the Blood Products Section of BoB (Dr. W. Boucher). Moreover, Dr. Douglas Kennedy (current acting head of the Blood Products Section), because of his limited period in office, was unable to provide much detail of the quality of previous audit activities and whilst Ms. Krepps diligently sought to "fill in gaps" it was evident that although she had worked in BoB for many years she had not been directly involved in Centre Inspections until January 1994. Moreover, because of her compliance function within BoB, Mrs. Krepps understandably found much of the author's questioning somewhat testing. It was also unfortunate that Mr. Bailey, recently appointed head of BoB, was on holiday at the time of my visit and that Dr. Aye (Medical Director CRC) was not available (on a visit to Vancouver) for background consultation on Centre outcomes of BoB's activities.

Thus it was that the primary source of data for the investigation were records made available by BoB staff. These files contained records associated with Centre licensing and included inspections notes and subsequent correspondence with Centre Directors and/or CRC Headquarters. Information was available from all CRC Centres; some was less complete than others (an occasional absence of inspection notes) and it was observed that all inspection notes were typed. There was no evidence of working (annotated) inspection notes. All files were briefly inspected but the following were examined in detail: St Johns, Newfoundland; Toronto; Hamilton; Ottawa and Vancouver.

Finally, the author is conscious that an important limitation of the visit was the time he was able to make available to the Commission of Inquiry. Any consequent deficiencies are regretted but hopefully somewhat compensated by the support and co-operation given by many, notably the current BoB team.

ISSUES TO BE ADDRESSED

In a helpful personal briefing note prior to the visit, George Connell advised that the following major issues should be addressed:

1. Are there standard review procedures in place which conform in quality and effectiveness to those prevailing in leading countries?
2. Are these review procedures applied effectively by responsible officers of the Bureau of Biologics?
3. Is there appropriate follow-up to ensure that products conform to specifications?

A RESPONSE TO THE CONNELL QUESTIONS

Whilst it is recognised that in January 1994 there commenced a quite radical and novel (in Canadian terms) inspection/audit initiative by BoB, directed towards CRC Blood Centres, in the light of the previous BoB track record in this area, the current limitations of blood product specifications in Canada and the available expertise and resource in BoB (all see below) it would be appropriate to conclude "NO" to all three questions posed by George Connell. Radical change is required and there is an urgent need for key policy and personnel matters to be concluded because the required change in culture both within BoB and the CRC may take some time to fully materialize.

SOME DETAIL ON MATTERS FOR CONCERN

1. Seemingly relevant historical perspective

Plasmapheresis has been regulated in Canada since 1978 but there is ample evidence in the BoB files that the quality of the BoB's contribution to this early regulation process was minimal. Inspections seemed to be remarkably sporadic and superficial - frequent reference is made to a "routine plant inspection report". The nature of this process must have had a negative impact on BoB and CRC staff or at least placed the audit of quality standards as a low priority in the Canadian blood supply system. Of no less importance, during this critical period between 1978 - 1989, when the quality culture should have been developing, is the evidence in the BoB files that Dr. Boucher's (the BoB chief inspector for blood centres) professional authority and competence was subject to challenge by Centre Directors either individually or corporately. Such behaviour must have had a negative impact on the morale of BoB staff (Blood Products Section) and/or encouraged them to avoid conflict by minimising the frequency of visits and/or deliberately avoiding areas of perceived contention. This latter development might also have led to the development of an inappropriately "cosy" relationship between BoB and CRC. There is evidence this may have existed.

It seems probable, therefore, that when the new legislation arrived in 1989, now bringing blood components into the Act, the culture and morale within the Blood Products Section of BoB was not well suited to the consequential tasks. Similar conclusions may apply to CRCS Centres and CRC HQ.

Finally, the Commission of Inquiry may wish to note in a regulatory impact analysis statement on the amended Act (published in the Canada Gazette part II Vol. 123 No. 8 p1 12th April 1989) that it was clearly signalled that the legislators envisaged annual inspections of CRC Centres by the BoB and this would "entail expenditure of resources within the Health Protection Branch". These annual inspections did not take place, apparently as a consequence of a decision made "at a high management level within BoB". I could find no records of this decision but did note that for most CRC Centres there was an inspection in 1989 and the next was in 1994.

2. Current Canadian Standards/Guidelines on Blood Collection/Component Manufacturing

Conversations with the BoB team revealed that the current Canadian guidelines on quality standards for blood collection and blood component manufacture were put together by two senior BoB staff in consultation with CRC staff. It is significant that the first publication was in 1992 and that there currently appear no plans for review/update. This contrasts with practice in other countries: in the U.K., for instance, the burden of the professional responsibility and initiative for the creation of these guidelines rests with the professional staff within the Transfusion Services. Work began in 1987 with the first edition being published in 1992. The U.K. equivalent of the BoB (the MCA) plays a minor/facilitating role in this exercise and this different emphasis has considerable merit.

It seems probable that the relative lack of expertise in blood transfusion practice within BoB, their limited manpower resources and historical relationships with CRC have much to do with the quality of the current Canadian Guidelines. In many areas these guidelines lack precision and detail and thus do not provide a sufficiently effective tool by which (CRCS Centre) specifications can be determined and audited against. Of particular note is an apparent absence of product quality control data indicating the tests to be carried out on blood components and the frequency of the tests. It was therefore not surprising to find no reference in any BoB inspection to the quality of blood components available from CRC Centres.

The rather modest reference to leukocyte depletion of blood components is surprising in a guideline published in 1992 and might suggest that some of the CRC experts were not consulted or, if they were, they didn't actively engage - Canada has a lot of expertise in this area!

PROPOSAL:

That urgent consideration be given to transferring to the CRC the primary responsibility for preparing, maintaining and communicating Canadian Guidelines for Blood Collection and Component Manufacture.

Such a development would find conceptional support in the Gagnon Report - Working in Partnerships - and would generate guidelines with much greater detail on specifications and quality control systems. The role of the BoB would be a low profile supporting one with, at the end of each revision cycle, a requirement to formally accept the guidelines as its base auditing specification. Consideration may well be given to involving the public in future exercises designed to develop national guidelines on blood collection and processing.

3. Proficiency Testing/Kit Evaluation

In the inspection reports examined there was no evidence found of CRC Centre proficiency testing, particularly in the areas of blood group serology and microbiology donation screening tests. During discussions with the BoB team it would appear that consideration is being given to the formal evaluation of microbiology donation test kits.

PROPOSAL:

The BoB should encourage/demand that the CRC establishes proficiency testing programmes that are open to BoB inspection. The development of a programme to maintain the quality of microbiology donation testing kits should also be encouraged though this could also be part of the CRC's overall quality programme. Continued reliance on the FDA licensing process may be disadvantageous to the future Canadian blood supply system.

4. Partnerships

The current investigation left the author with a feeling that, in the past, the Blood Section of the BoB has been, in the context of CRC Centre inspection skills/practice, rather parochial and has not sought to participate in information/experience/training exchange with its counterparts in the USA and other countries, particularly those operating national blood transfusion services. Much valuable expertise can be acquired by such endeavours and lead to a much needed boost in professional confidence - and at low cost.

PROPOSAL:

that BoB managers explore ways in which they can establish partnership arrangements with other countries. Particular attention might be directed towards the MCA in the UK: the author would be pleased to assist in the development of what would be a professional benchmarking exercise.

5. The Inspection Process

From the records and discussions with the BoB team, there were a number of causes for concern with regard to the audit/inspection process. These can be summarised as follows:

(a) Planning

The BoB team have insisted that the audit team should arrive at the Centre unannounced - "to stop them fixing things in advance". This must surely represent a grave defect in current attitudes. This culture is seriously counter productive to the development of modern quality systems.

PROPOSAL:

that advanced (open) planning of audits is introduced as soon as possible.

(b) Basic GMP

There was little evidence in the available files that, until the 1994 audit, much attention had been directed towards basic GMP in the CRC Centre inspections. Whilst there appears to be significant management problems following the introduction of some of the Field Operations Directorate staff (see below) into the BoB Blood Centre Audits there was ample evidence of the substantial enhancing effect of their contribution (notably GMP audit) to the 1994 audit. This professional development should be encouraged and may provide important opportunities for the future.

PROPOSAL:

that further consideration is given to the integration of elements of the Field Operations Directorate staff into the Blood Products BoB team.

(c) Grading of Deficiencies

There was no evidence in the Audit Reports or in the follow-up letters sent too CRC Centre Directors that the BoB team had prioritised deficiencies. In the U.K. they are classed as Critical, Major and Minor. Such gradings are important to responding Centre managers for they signal the expected speed of response and perceptions of the severity of deviation from acceptable standards. Similarly, there was no record in the reports as to when BoB inspectors expected a timeous response. This came as no surprise for the time intervals between inspection and issue by BoB of written reports, even following the January 1994 inspections, were of several months (3-4). This is unacceptable practice and needs to be reviewed.

PROPOSAL:

that arrangements are put in place to reduce substantially the time between the audit and issue of formal reports and that deficiencies are graded according to severity and

timeousness of response.

(d) Follow-up Process

There was little reference in the reports or correspondence from all the BoB (Blood centre) audit activities since 1989 of effective, or indeed any, follow-up. This must be regarded as lamentable and if the records reflect practice then it is unlikely the CRC Centres have responded effectively unless CRC HQ is playing an internal "policing" role.

PROPOSAL:

that effective follow-up systems be developed as soon as possible.

(e) Information Technology: Computer Systems

Much effort in the current audit process of blood transfusion Centres in some countries is being directed towards IT/computer systems. I found little evidence of this activity in the 1994 Canadian BoB audits.

PROPOSAL:

that the development of appropriate IT audit is introduced as soon as possible.

(f) Training

There was ample evidence in BoB that insufficient attention has been paid to appropriate training of staff and similarly insufficient attention paid to assessing CRC Centre Staff's training and professional competence.

PROPOSAL:

that training should be a feature of future programme developments.

(g) Checklist for Inspections

There appears to be no detailed checklist (standard format) within BoB which goes some way to ensuring that all Centres are inspected to the same standard. As a consequence and because the inspections have been very infrequent and carried out by different individuals, there may be significant variation in quality standards between Centres which originates from the performance of BoB.

PROPOSAL:

that there should be urgent attention given to the creation of a standard format for inspections and these should be made available to the CRC Centres.

(h) Adverse Event Reporting

No reference to this topic appeared in any reports inspected.

PROPOSAL:

that inspection of adverse event/error reporting systems should be included in all inspections.

(i) Locus of CRC HQ

In a number of Centre letters the author had the distinct impression that part of the BoB team's response was directed to the national CRC HQ. For instance, in 1991 the BoB team referred again (they commented in 1989) to their concern (in Toronto) at the lack of staff to permit acceptable donor selection - but signalled to the Centre that it should liaise with CRC HQ to determine the time frame for response! Similarly, whilst the letter from BoB to the Hamilton Centre, following the 1994 inspection, is to the Centre Director the response came from Dr. Aye (CRC HQ)! Whilst CRC HQ must be aware of BoB inspection outcomes, there must be no diminution/confusion in lines of responsibility between the Centre and BoB. At present this seems to exist and is increasing (see below).

PROPOSAL:

that in the context of BoB Centre Inspections consideration should be given to diminishing the interface between BoB and CRC HQ and enhancing that between BoB and the CRC Centres. The recent proposal from BoB to institute management arrangements in which the Centre QA Managers would report directly to CRC HQ QA Manager (and not their local Centre Director) should be withdrawn/reversed. In the author's view this proposed new arrangement is not in the best interests of the development of effective quality systems throughout the Canadian blood supply system. Beyond this, BoB should do more to encourage CRC HQ to develop the internal audit process throughout the CRC and inter-Centre auditing exercises.

6. BoB Management Process

It has been difficult not to conclude that there have been significant deficiencies in the management process associated with the inspection of Canadian Blood Centres ever since there has been a legal requirement to institute some form of quality standards (1978). These deficiencies seem to have existed at all relevant levels within the Health Protection Branch. In particular, poor systems of accountability and a remarkable lack of sensitivity to and interest in the work of subordinates has been evident.

More recent managerial actions have led to a further deterioration in morale within the Blood Products Division and there is now an urgent requirement to create a new team which is

exclusively dedicated to the blood supply system and that is in close constructive contact with colleagues in CRC and other regulatory colleagues in the same business, world-wide.

Finally, it seems probable that more attention should be given to harnessing the assistance of local Field Operations Directorate personnel. This could be of particular value in the development of effective follow-up processes.

CONCLUSIONS

Canada, as in many other countries, has not been optimally served by those responsible for regulatory affairs associated with local blood supplies. The evidence in support of this conclusion is overwhelming and it is difficult not to conclude that, as a consequence, significant and inappropriate quality deficiencies may exist in some parts of the CRC.

The good news is that recent events have led those responsible for these quality systems to recognize the nature and magnitude of the deficiencies and, as a consequence, efforts are already underway to address the problems.

It is proposed that the current process of addressing the problems might be better focused and targeted and that this should be achieved by the creation of a small BoB team that is exclusively concerned with all quality aspects of Blood Supply Centres and the active development of partnerships that are of benefit to the BoB team. In this latter regard the CRC Blood Services and similar regulatory teams in other countries should be strong candidates as partners. As regards the expertise of the small BoB team: it should be founded upon knowledge and experience of GMP, GLP and GCP with much evidence of good management practices and an avid desire to acquire knowledge about blood transfusion practice.

**REPORT OF VISIT
TO
BUREAU OF BIOLOGICS, HEALTH CANADA**

SEPTEMBER 7-9, 1994

By John S. Finlayson, Ph.D,
Associate Director for Science
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Introduction, Statement of Task and Comments

My visit was in response to an invitation from Dr. G. Connell, Principal Advisor to the Commission of Inquiry on the Blood System in Canada. The invitation stated in part: "One of our [i.e., the Commission's] responsibilities is to examine the performance of the Bureau of Biologics as it bears upon the safety of blood products and services. This will require a review of selected files of the Bureau which deal with new product submissions." A subsequent letter re-emphasized that "the task...would be to review selected files and to report to the committee as to the overall quality of the work of the Bureau and its contribution to risk reduction." These statements formed the basis of my understanding of the task. Fulfilling this task, I decided, would require:

- (i) learning how the Bureau has operated and currently operates in the course of regulating plasma derivatives--particularly with respect to receiving, reviewing and arriving at a decision about a new product submission.
- (ii) learning what guidance was and is available to reviewers, how it becomes available, and how new reviewers are brought into the review process.
- (iii) actually examining selected submissions and the ensuing documentation (be it correspondence, review memoranda, etc.)
- (iv) developing, in the context of i-iii, a feeling for the similarities and differences between the Canadian and U.S. systems for accomplishing the regulation of plasma derivatives.

The last part of this report presents recommendations. Both the report and the recommendations, however, extend beyond the boundaries of the task as stated above. This extension was considered not only permissible, but actually desirable inasmuch as a national biologics regulatory agency is (or, if it is to be effective, should be) a highly integrated operation.

Caveats

A current list indicates at least 16 plasma derivative manufacturers that are licensed in Canada. These, in turn, are approved for approximately 50 products. Moreover, other submissions that did not result or have not yet resulted in licensure have been reviewed at the Bureau of Biologics. In the course of a few days' examination, only a fraction of the available material can be seen in detail. Accordingly, an impression must be drawn on the basis of a very small sampling.

It goes without saying that an exhaustive evaluation would virtually require re-reviewing the entirety of each submission file--clearly an unrealistic concept. One must therefore accept *a priori* the potential criticism that the examination has been less complete.

Timing of Visit

My arrival on September 7, 1994 coincided with a crisis¹ which required the attention (and, in many cases, travel off-site) of many key staff members. Accordingly, I had limited access to Dr. K. Bailey (Director, Bureau of Biologics), very limited access to Dr. D. Kennedy (Acting Chief, Blood Products Division), and was not able to meet with Dr. P. Neumann (Head, Coagulation Section) at all.

The remaining staff was clearly being required to shoulder the added responsibility. Nonetheless, to the extent possible, Ms. P. McKnight (Regulatory Advisor, Compliance Division), Dr. M. Davis (Senior Advisor), Ms. S. Blakely (Laboratory Technician, Coagulation Section), Ms. H. Chong (Biologist Evaluator, Plasma Derivatives Section), Dr. F. Hindieh (Head, Blood Banks Section), and Dr. A. Ridgway (Head, Biotechnology Section) were extremely generous with their time.

Modus Operandi

I interviewed staff members to whom (and to the extent that) I had access and obtained various guidance documents ("Regulatory Framework") in an effort to understand the procedures employed in the regulation of i) biologics in general, ii) blood products more specifically, and iii) plasma derivatives in detail. During the first 1.25 days I was accompanied by Dr. P. Chan, who is assisting Dr. Connell and who had provided numerous background documents, including the compiled Regulatory framework. At several points during that time we discussed the scope of the task and issues raised during the interviews. Dr. Chan and I were taken on a tour of the laboratory facilities of the Blood Products Division by Dr. Ridgway. This tour permitted a view of the physical facilities and the equipment, and afforded an opportunity to meet some junior staff. Much of the remainder of the visit was spent in reviewing files, i.e., documents submitted by manufacturers and records of the Bureau of Biologics' reviews and responses. (The files selected for Examination dealt with plasma derivatives, some of which are licensed in Canada and some of which are not.) However, I did return to the Blood Products Division laboratory area to speak briefly with reviewers and laboratory workers, and to Compliance Division for more extensive discussion (as schedules permitted) of specific aspects of biologics regulation.

Specific Observations

Results of File Review. The sampling used in the review, which was conducted over a period of two days, involved two product classes (immune globulins and clotting factors), four different

¹ The Canadian press had "discovered" that the U.S. FDA had inspected a Canadian Red Cross blood establishment more than a month earlier and had left a 19-point Notice of Findings. This was receiving national news coverage and was evoking calls for resignation of the Health Minister, who had summoned key personnel to assist in her response to the outcry.

regulated firms, specific products that have been licensed in Canada, and specific products that have not been licensed in Canada.

The first day's impression was that the files were smaller than those submitted for comparable (or the same) products in the U.S. This, as clearly explained in response to my inquiry, was an erroneous impression. It was created by the fact that, because most files for most products are actually voluminous, only a portion of the material is kept on-site (i.e., in the files of the Compliance Division, Bureau of Biologics). The rest of the material for a given file is listed in a computer database (maintained in the Compliance Division), packed in numbered boxes, and stored off-site in Ottawa by a commercial contractor. I was told that in case of urgent need a box can be retrieved within an hour. Routinely, material is retrieved within a day, e.g., requested in the morning, delivered in the afternoon. I gave a specific example and was shown, by computer, where the material was located and with what it was co-located. Material pertinent to more than one file may be in a single box (approximate dimensions 50 cm x 30 cm x 30 cm) and that pertaining to a single file may be housed in more than one box. However, the contractor does not open boxes or rearrange the material therein; that is done only by personnel at the Bureau of Biologics. In the interest of time, I did not request any material from off-site.

In response to inquiry I was consistently told that only important material is kept on-site, but I surmised that a considerable amount of individual judgment is exercised. For example, in one fairly extensive response to a review, the manufacturer submitted narrative answers supported by addenda (photographs, graphs, tracings from laboratory instruments, etc.). The narrative was stored on-site; the addenda was housed off-site. On the other hand, on-site files often contained two (or even three) copies of the same document, product package label, etc.--clearly neither an efficient use of limited space nor a practice consistent with the intent.

Other filing idiosyncrasies included the finding that a given product made by a particular manufacturer might have several files (reasonable, if they represent different kinds of submissions made at different times) indexed under several titles--e.g., trade name first, generic name first, generic name only (not reasonable and somewhat confusing). Some files were indexed with a suffix "C" (meaning "clinical data"), whereas in other cases the clinical information was included in the regular file. Some files bore a suffix "A" ("adverse reaction reports"); these exhibited considerable heterogeneity. For example, one contained many reports but no indication of follow-up of Bureau of Biologics review; another contained a single case report with fairly extensive follow-up or Bureau of Biologics review; another contained a single case report with fairly extensive follow-up. All dated back to a period in which the product was not licensed because the Bureau of Biologics does not receive adverse reaction reports for approved products. Those are sent to the Bureau of Pharmaceutical Surveillance, except for adverse reactions to vaccines, which go to the Laboratory Centre for Disease Control (see Recommendations).

For the files that I examined and the product range that I was able to cover (and which while I chose on the basis of their importance and complexity), the quality of the reviews appeared remarkably good--especially in view of the limited staff available. Unfortunately, even that level may have eroded. In virtually every case in which I wished to meet with a reviewer (e.g., to

question him/her about a particular statement, to inquire about subsequent developments regarding the product or the firm, or simply to share review experiences) I learned that the reviewer had resigned or retired. This was true both for manufacturing/testing and clinical reviews. Almost the only exceptions were clinical reviews performed by outside contractors--who also were not readily available.

In some cases reviews were conducted with surprising speed (e.g., stability data submitted, received, and reviewed--all within a matter of a few days). In others the intervals indicated that the submission had waited in queue and the review itself had gone slowly. Certain situations, which do not appear to have been isolated events, were particularly noteworthy. One scenario was the completion of the review of a particular submission but a failure to communicate the results to the manufacturer. It was not clear where in the chain of reviewer to supervisor to Compliance Division to manufacturer that the breakdowns had occurred. A second scenario was the completion, or virtual completion, of review for a particular product but licensure never being achieved. (It must be emphasized that merely completing review of the paperwork does not guarantee licensure; pre-licensing inspection, testing of conformance lots of product, and preparation of final labelling are among the critical steps needed to complete the process. Nevertheless, the files gave no indication of deficiencies encountered at these late stages.) The staff seemed to be well aware of this situation and to have envisioned a cogent strategy for managing the submissions that are immobilized in it. However, inasmuch as unavailability of personnel to complete the licensure process created the problem, it is unlikely to be solved until sufficient staff (and sufficiently experienced staff) are available to implement that strategy.

Results of Interviews with Laboratory and Review Personnel. During the laboratory tour on September 7, 1994 I availed myself of the opportunity to discuss the laboratory approach to biotechnology product regulation. I had noted that the Bureau of Biologics can, and often does, receive the product when the review is at the IND stage. This is common practice in the Biotechnology Section. This allows the staff to develop "hands-on" familiarity with the product, to learn its characteristics and idiosyncrasies, and to evaluate the importance, usefulness, and reliability of lot release tests that the manufacturer has proposed (or, in some cases, failed to propose) before a New Drug Submission is ever made. This is a highly commendable approach and, in the face of apparently unrelenting pressure to decrease lot release testing, may represent one of the best uses of laboratory personnel.

Because most of the files I examined had undergone relatively little recent review activity (see above), I was interested in learning about products under current review. I found that at least some review personnel have a sufficient breadth of knowledge and experience to cross not only "submission lines" (i.e., by dealing with INDs, New Drug Submissions, and license amendments), but also product lines and section boundaries as well. This is very much to be encouraged, and such "broad spectrum" personnel are extremely valuable for instructing new recruits. From the nature of the discussions, the responses given to my questions (both review-oriented and laboratory-oriented), and the questions I was asked (mostly about U.S. review experience, product status, test methodology, and reference standardization) it was clear that the quality of effort being brought to the regulatory task was very high. However, despite the knowledge, versatility,

and obvious commitment to the organization and the work, submissions were still waiting in queue simply because a sufficient number of capable personnel were not available.

Differences between Canadian and U.S. Systems for Biologics Regulation. This section is obviously not the result of a comprehensive study, which, if conducted at all, would require a team with a wide range of scientific, medical, administrative, and legal skills. It is rather a summary of observations made in the course of other aspects of the visit. Moreover, either casual observation or comprehensive study would reveal many similarities between the two systems--not the least of which is an effort to develop written guidance documents for areas in which none had previously existed. Accordingly, similarities are not discussed here.

Some of the differences are driven by difference in legislation, regulations and paperwork forms, all of which are structured differently in the two countries. For example, in the U.S., separate forms exist for INDs and Product License Applications, and the forms for the latter are product-class-specific. In Canada, the same form is used to initiate any of a number of different kinds of applications (e.g., a New Drug Submission, a Supplemental New Drug submission, and IND) and to cover all products. Furthermore, if a particular biologic is not considered a new drug, no New Drug Submission is required and the necessary information can be described in an Application for Licence, which bears some similarity to a U.S. Establishment License application. Operationally, some of these differences may be more apparent than real. However, for biologics, even seasoned personnel expressed confusion about the basis for deciding whether a particular product is a "new" or an "old" biological drug. (Part of this difficulty stems from the fact that the Canadian system is heavily oriented to pharmaceuticals; consequently, biologics--and their unique problems--are always struggling for recognition and a voice within that system.)

Probably the most conspicuous difference, at least in the regulation of blood products and plasma derivatives, is that U.S. reviews tend to be done by ad hoc committees, the size of which varies with the complexity of the submission, whereas Canadian review has traditionally been performed by one person or, at most, one non-clinical and one clinical reviewer. This approach developed, in part, out of necessity (a small staff, a large workload) and, in part, by design (reflecting the "vertical channelling" management style of Dr. J. Furesz, the previous director of the Bureau of Biologics). It was consistent, for example, with the practice of having only a small cadre of biologics inspectors (4 or 5 out of a staff of 66). In addition, there has been heavy reliance on outside clinical reviewers, who are hired on contract. Although most potential contract reviewers express interest in pharmaceutical rather than biologics review, Dr. Davis estimated that about half of the biologics reviews are performed by outside reviewers.

Conversely, whereas the Center for Biologics Evaluation and Research (CBER) makes liberal use of its product-class-oriented advisory committees composed of outside experts, the Bureau of Biologics lacks such a resource. Although an external advisory committee was appointed approximately eight years ago, it has no function in the review process analogous to that of the CBER Blood Products Advisory Committee.

Finally, unlike the U.S., Canada has a requirement that manufacturers must make yearly application to renew their licenses. Although this appears to be a sound idea (i.e., it could result in culling out "dead" files and avoiding "empty" licenses that do not represent true manufacturing activity), it is very demanding on the time of personnel in the Compliance Division, and annual renewal deadlines are frequently violated. (In actual practice, this difference between the countries may diminish if U.S. manufacturers of User Fee products choose not to pay the annual maintenance fee for inactive licenses.)

Overall Impression

My general impression is one of an organization that is vulnerable, if not utterly fragile. Many senior people--and, consequently, their institutional memories--have left. Repeatedly, during the course of file review, I asked if I could speak with the person who performed and signed the review and was told that he/she had resigned or retired. Many people in very responsible positions have been with the organization for only a short time; junior staff with considerable laboratory responsibility have, in some cases, been in their current positions for only a matter of months; many positions are occupied by non-permanent employees; and some positions are not occupied at all. To cope with this situation, personnel have been moved between sections and divisions. They seem to have responded in a willing manner. Moreover, this "filling in" has had the beneficial effect of broadening individuals' scope and skills. However, these ad hoc rearrangements have created an even greater sense of instability. Underlying all of this is the fact that the Bureau of Biologics in general and the Blood Products Division in particular are woefully understaffed. (In the words of one employee whose responsibilities cut across all segments of the Bureau of Biologics, "The Blood Products Division has the Bureau's smallest staff and its largest product load.") As a result, there is a staggering backlog, which persists in the face of a constant influx of submissions dealing with current products and an accelerating growth of new ones. In addition, the organization appears to be under heavy criticism, if not actual siege. Moreover, its paradigm for operation (viz., an integration of research, review, testing, and inspection), which has been its strength, is being questioned--and many of the staff feel that the questioners have neither recognized the purpose of the organization nor come to grips with the rationale for that paradigm.

Accordingly, management's task becomes not only to address specific operational matters so as to remedy problems (e.g., the backlog), provide a smooth-working system, and offer structure and guidance for the future, but also--in an immediate and urgent manner--to preserve and nurture what could best be described as a fragile ecology or an endangered species.

Conclusions: Statement and Format

If the functionality of the organizations (meaning the Bureau of Biologics, Blood Products Division, and Plasma Derivatives Section) are to be i) preserved and ii) enhanced, in that order, there must be a sustained commitment to i) rebuilding and ii) building. There appears to be a small number of very knowledgeable and extraordinarily dedicated junior staff who have been with the Bureau of Biologics long enough to have a clear sense of both its operation and its

mission. This is the obvious nucleus for the building program. The challenge for higher management will be to deploy and use this nucleus wisely, in full recognition of the multiple functions (e.g., teaching, learning, developing written guidelines, inter alia, while dealing with the multifaceted daily workload) that these junior staff members will be asked to perform.

The following sections have been divided into "recommendations" and "imperatives." Recognizing the possibility for overlap (i.e., a high-priority recommendation could be considered an imperative), I have employed the following definitions:

- | | | |
|----------------|---|--|
| recommendation | - | an important concept that should be implemented |
| imperative | - | a concept that cannot be granted the luxury of tranquil rumination but which must be implemented with emergency-room-like swiftness and attention. |

In some cases the steps proposed, or similar steps, may have already been undertaken. I have made no attempt to avoid this redundancy. Where it occurs, it may be considered an endorsement of the building program's direction.

Recommendations

1. Strengthen the clinical review capabilities of the Bureau of Biologics, especially those of the Blood Products Division.
2. Strengthen biostatistical support for product review by (inter alia)
 - a) increasing the number of biostatisticians judiciously, as needed
 - b) raising the sophistication of review and laboratory staff in statistics so as to
 - i) increase appreciation for the kinds of questions that statistics can and cannot address
 - ii) enhance ability to pose questions in terms biostatisticians can readily apply
 - c) raising awareness of biostatisticians of "real world" problems faced by the review/laboratory staff
 - d) bringing biostatisticians into the review (or testing, or standardization) process as early as possible.
3. In the course of accomplishing 1 and 2, take care to accomplish two seemingly opposed objectives, viz.:

- a) provide opportunity for clinical reviewers to interact with each other so as to share ideas, new information, and new methods
 - b) provide the same opportunity for biostatisticians, but
 - c) avoid, at all costs, isolating either biostatisticians or clinical reviewers so that they interact only among themselves. Integration of each into the overall function of the Bureau, divisions, sections-manufacturing review, testing program, research, guidance document development, etc.--is the key to a viable operation.
4. Involve more than one person in each manufacturing review (at least of the more complex submissions). This will provide instant back-up, useful redundancy, generally broader reviews ("two heads are better than one"), and training opportunities (younger/newer reviewers can see more than one approach simultaneously; older/experienced reviewers benefit from others' contacts, reading, research, etc.).
 5. Involve more than one person in each review of clinical data. Not only products and clinical trial designs, but also therapies have become more complex. For example, two or three drugs/biologics may be used together; a biologic may be used with or after a surgical procedure; etc. More than one person's expertise and critical insight are often needed.
 6. Devise a format for making the details of clinical trial results available publicly. Current Product Monographs contain much information, but the clinical sections are very brief and often quite general. Most physicians, even those working in academic or other teaching hospitals, currently receive only information they read in the medical literature, which can present a very selective picture. Since clinical trial data of approved biologics are already available on request, implementation of this recommendation should be straightforward.
 7. consider a mechanism to make detailed clinical trial information available publicly if a biologic is not approved. This will be more difficult, but would be an important contribution.
 8. Encourage "pre-meetings" (e.g., pre-INC submission or pre-NDS). If joint review is contemplated, there might even be participation (by conference call) of CBER. Although the meeting privilege can be abused by manufacturers, such meetings are, on balance, mutually beneficial. This is not a new recommendation. Dr. P. Percheson, Chief, Bacterial Products Division, made it emphatically at a meeting in Washington in 1992--but then he left the Bureau.
 9. As greater effort is made to formalize and meet review timelines, and as the new computer system is being implemented, build into the software tickle files that can be accessed "backwards". That is, the database for a given product file contains the information that the first review is due by ...(date). This is already displayed when that

file is requested. "Backwards" implies an interactive system which could be queried: "Today is 1 October, 1994; which biologics (blood products, plasma derivatives, etc.) reviews are due today? this week? this month? Which follow-up stability (clinical, etc.) data are due from which manufacturer/for which product today? this week? this month? are overdue?"

10. Develop a system to insure that when a review is completed, the results will be communicated expeditiously to the Compliance Division and, equally expeditiously, to the manufacturer.
11. In parallel with recommendation 10, develop a system to assure that information provided by manufacturers in response to direct requests from reviewers will ultimately be placed in the Compliance Division's central file.
12. Consider streamlining the annual license renewal in such a way as to provide timely notification to manufacturers and minimize the paperwork burden on Bureau staff, while assuring that the information submitted is accurate, current, and complete.
13. Devise an information-flow system (even if only a very simple and informal one) among the Bureau of Biologics, the Bureau of Pharmaceutical Surveillance, and the Laboratory Centre for Disease Control to assure that information (e.g., adverse reactions to a biologic product, product recalls, outbreak of blood-borne disease) arriving anywhere within the system will be transmitted quickly to the person(s) best equipped to act.
14. Encourage the laboratory and review staff at all levels to interact with their peers at other regulatory agencies.

Imperatives

1. Provide sufficient staff to deal with severely backlogged, growing field.
2. Utilize that staff appropriately, through training (primarily on-the-job), deployment, interaction (with supervisors, with employees in other sections and divisions); allow participation in a variety of activities (so as to broaden skills and build in back-up).
3. Retain that staff. This is critical at all levels; much management effort will be required to convey the message that their apparently Sisyphean task is important and not hopeless.
4. Maintain/extend the skills of that staff. This imperative is closely tied to 2 and 3. It is necessary to train, enhance by constant feedback, encourage, reward. Maintain laboratory skills and expertise by all means available, including participation in workshops and symposia. Do not create either the reality or the perception that administration is the only route to job success or satisfaction.

5. (NOTE: This is both an organizational and a personnel imperative.) Strengthen, do not lose, the research function. Maintaining and enriching it is an important way--and may be the only way--to
- a) deal with the new-era products
 - b) maintain scientific credibility with regulated manufacturers
 - c) retain a scientifically oriented, astute staff
 - d) address product crises--regardless of whether "new" or "old" biologic drugs are involved.

Caveat: Do not attempt to compete with universities or even with manufacturers' drug development programs. Concentrate on that research which the Bureau of Biologics is in a unique position to perform.

6. Integrate the function of the Bureau of Drug Research with that of the Bureau of Biologics and other product-oriented organizational units.

The foregoing report is, within the constraints noted above, complete and, in my best judgment, accurate. Although I have discussed some of my observations with staff at the Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, and notwithstanding the facts that this visit was conducted and the report prepared as part of my official duties, the observations, evaluations and recommendations are my own and do not represent those of the Food and Drug Administration.,

APPENDIX VI

**INSPECTION REPORTS FROM
MONTREAL, SAINT JOHN AND WINNIPEG
REGIONAL BLOOD CENTRES**

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COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL INSPECTION TEAM
SUMMARY REPORT, NOVEMBER 1994

1. REMIT

The purpose of the visit was to use an independent team of international, experienced auditors to establish whether the Centres visited had systems to ensure a safe blood supply and to determine the extent to which GMP systems had been implemented and were being complied with.

2. SITE SELECTION/LIMITATIONS OF PROCESS

Three sites were visited ie Montreal, Saint John NB and Winnipeg. The auditors had no insight into the selection process for these sites, other than an understanding that they were sites that had not previously been visited by the Committee, (although on one visit, the Director volunteered that the sites had been selected because they were the three best!) Considering this background, it is for the Committee to put the auditors' findings into context against the diverse standards that were found to exist across only 3 of the 17 Centres.

It also must be acknowledged that any audit can only give an insight into the practices viewed and discussed during the audit process. Audits represent only a "snap shot" in time and must be interpreted against that background.

Largely to satisfy the requirements of the Committee but also to ensure the scope of each audit was comparable, an audit checklist was produced. This was based on critical control points in the process that extends from donor recruitment through to release of components for transfusion or for further manufacture. The checklist was based on international best practice documented in available international codes and standards and from the auditors' own experiences.

Whilst not used, *per se*, as a "ticklist", these checklists proved a useful aide memoir and were completed for each inspection.

3. THE AUDIT PROCESS

The audit process was conducted in a sensitive but very thorough process in line with the format that is followed by Regulatory Bodies throughout Europe and Australia and has been adopted by the Scottish National Blood Transfusion Service. The collection of detailed, objective evidence was considered essential to provide the Committee, auditees and auditors with a clear understanding of system problems and to

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provide auditees with every conceivable opportunity for improvement. This detailed and objective collection of evidence of compliance also provided the auditors with a factual base on which to analyse and report problems in the system.

The auditors' approach was to grade recorded deficiencies into three categories ie principal matters of concern, other major matters of concern and other matters of concern. Whilst allocation to a particular grade was not an exact process, it provided a useful means of assessing the overall security of each system and helped auditees prioritise deficiencies into a logical corrective action programme.

4. GENERAL OUTCOMES OF THE AUDIT PROCESS

Throughout the audit process it was abundantly clear that the Canadian Red Cross Blood Transfusion Services are fortunate to employ so many quite excellent, well motivated staff who were, in spite of the present difficulties, eager to do a good job and keenly interested in how they could do it better.

The auditors were appreciative of the very cordial and interactive manner in which they were allowed to function, not least because this optimised any benefits that the process might deliver. It also is important to note that with respect to deficiencies identified during the process, the auditors were in complete agreement (although this is hardly surprising since the concept of GMP in Blood Transfusion is an entirely generic concept).

It is, perhaps, more notable that none of the deficiencies raised by the auditors were questioned by the auditees. Whilst, further detail often was requested and given, the vast majority of deficiencies were acknowledged as being activities that represented non compliances with the principles of GMP. When viewed positively, the deficiencies were seen as opportunities for improvement that would ensure the delivery of a more carefully controlled and even more secure, blood supply sub system for Canada.

Summary and detailed audit reports are attached for each of the sites visited. These record a high level of professionalism and commitment amongst staff which contrasts with the present difficulties and the many frustrations being caused by the overall management arrangements for the Service.

It was clear that much effort has been expended to develop an understanding of, and systems that comply with, GMP. This independent inspection process has produced an insight into how much has been achieved (for much **has** been achieved) and how much remains to be done (Quality is a journey, not a destination!).

A number of important GMP non compliances were recorded on each site.

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However, there was clear evidence that, for those systems that were considered absolutely crucial, ie collection, testing and release, the sites visited had secure systems that ensured the provision of a safe blood supply.

Clearly, individual Centres varied in their effectiveness and some fairly serious problems were uncovered, many of which led back to National HQ. Indeed, it would be appropriate to suggest that system security is being achieved in spite of, rather than because of, National HQ and that is a most unfortunate situation.

Whilst review of the inspection reports for each visit will provide the reader with an insight into the relative weaknesses and, by omission, strengths of each Centre, it would be wrong to draw conclusions by adding up the numbers of defects reported. This overly simplistic approach could create a false impression since each audit, however well structured, is a separate entity and should be viewed as such. General comparisons are possible but firm conclusions should be drawn with extreme care.

Across the sites visited the extent of GMP compliance varied between departments. Elements of the systems viewed ranged from poor to a standard of excellence that ranked in the top league of systems previously experienced by the auditors. Some purely illustrative examples are as follows:

- . Arrangements for QA in Montreal were excellent whilst in Saint John and Winnipeg, conceptual understanding was at a much earlier stage of the process and the QA specialists had insufficient knowledge/training/responsibility and authority to function effectively as a QA Manager within a system of GMP.
- . TD testing labs in Saint John and Winnipeg were excellent as was the donor grouping lab in Winnipeg. Unacceptable, old equipment was a major GMP problem in the Saint John blood grouping lab (in spite of which they were functioning very securely). Nursing/collection team standards were very high in Saint John and Montreal, less so but developing in Winnipeg.
- . Component processing tended not to follow GMP principles and "open processing" procedures were especially poor. Storage of blood components and products and general storage of supplies were not good.
- . Premises at Winnipeg were unsuitable for a variety of reasons and Montreal was operating on four sites - hardly an ideal situation. Saint John had much equipment that was well past its replacement date.
- . Lack of an effective, fully integrated computer system was a major problem being overcome by excessive transcription of results and manual cross checking.
- . A surprising number of important health and safety concerns were raised.

The response of staff to the manner in which these deficiencies were identified, discussed and recorded was one of genuine appreciation. This, of itself, gave enormous credibility to the process.

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5. IMPEDIMENTS TO PROGRESS

The Canadian Red Cross Blood Transfusion Service wishes to develop, implement and maintain Quality Systems that are based on compliance with GMP and the principle of continuous improvement. **Whilst this audit process has disclosed a number of non-compliances, it also has revealed a number of impediments that must be addressed before the ultimate objectives can be pursued in a more timely and effective manner.** These can be summarised as follows:

5.1 LACK OF CLEAR OBJECTIVES/STANDARDS

Staff are unclear as to which standards they should be following - BoB, National, FDA featured in almost every combination. There was evidence of inconsistencies which led to confusion.

It seems inappropriate that BoB should approve SOPs eg for donor exclusion and TD testing. This adds an unnecessary layer of bureaucracy which delays implementation and revision. As an example of this, equipment for on line printing of labels for source plasma was viewed in all sites. This had been available to the Centres for over a year but had not been introduced because of delays in validation/approval by BoB.

These problems are important and must be addressed.

5.2 NATIONAL: SOPs, DIRECTIVES AND POLICY SETTING

From the principal matters of concern in the audit reports it is hard not to conclude that the manner in which National office currently operates is a major impediment to GMP. Furthermore, from the evidence seen and recorded, their understanding of GMP, perhaps even of the core systems needed to run an effective, efficient blood transfusion service, must be considered questionable.

However well intentioned and committed the National team are, it was clear from our audits that as a unit they were, at best, ineffective eg

Directives were being sent that made unreasonable demands for rapid, excessive, and, at times, ill conceived change. This in turn created unacceptable pressures on staff and on their developing systems which often necessitated breaches in GMP if they were to comply within the deadline set. At various points in time the auditors recorded indecision, delay and a complete lack of communication from National. This apparently autocratic approach created frustration, bemusement and resentment and it must be assumed that the National Office are oblivious to the problems they are causing. Without probing for answers, it would be reasonable to assume that

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staff opinion of National is not high! Furthermore, the notion that controlling operations through National SOPs will produce a generic system is a fallacy. At audit, three different system had been developed to cope with often vague "outline" SOPs issued by National. eg each Centre had a different system to identify components that had been approved for issue. Consequently, imported components carried the originating Centre's issue approval symbol which differed from the symbol used at that site. This could be very confusing for customers and should be governed by a National policy.

It is considered that redefining the roles and responsibilities of the Centres and National HQ could greatly improve efficiency and performance eg

National HQ should co-ordinate the development of National policy and strategic planning. They should provide support and guidance to Centres and develop effective mechanisms to monitor and review progress. National should not issue SOPs as at present.

Individual Centres should be responsible for implementing National policy through locally developed and controlled procedures.

5.3 GMP

Overall, comprehension and implementation of systems that comply with GMP could best be described as embryonic. Training for QA specialists in Centres was limited to a 3 day introduction to cGMP using the Ortho Diagnostics training manual/ system and, more recently, a 3 day training session on audit. In two of the three Centres visited, **QA Specialists were only beginning to grasp the concepts of GMP but they had insufficient knowledge, responsibility or authority to function effectively as QA Managers in a GMP environment.** That said, these individuals were already being required to deliver cGMP training to other members of staff.

Given the current situation (in the broadest sense) it is probably too early to give GMP training to all staff ie it may be better delaying this until the environment is more conducive to implementing a GMP approach throughout the service.

There was concern that plans were in hand to convert the QA Specialist role to that of QA Manager and, concurrently, to change their reporting lines from Centre Director to National Office.

Firstly, it must be acknowledged that the role of a QA Manager is (or should be) much more demanding than that of a QA Specialist and it is wrong to assume that individuals currently in post (as QA Specialists) will have the additional key attributes for the new, much more demanding position.

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Secondly, the proposal to change reporting lines could have serious repercussions for the effective function of local Centre teams. The importance of this cannot be overstated since already there was evidence that QA Specialists were being viewed by their peers in a very negative way. QA personnel have a key role to play in supporting, encouraging and co-ordinating local teams. Any plans that interfere with such essential activities could, at best, be counterproductive.

There was too much emphasis on inspecting out errors and too little on prevention ie quality was not being designed into the system. Clearly, this indicates that error management systems need improvement.

There was concern that there was too much change, much of which was being enforced by National, much in response to deficiencies identified at inspection. Change should be necessary, planned, controlled and validated before implementation, and reviewed afterwards. Unless these "rules" are applied, too much change, especially under pressure, can be dangerous. During the audits, there was concern that this was the case, especially in the Winnipeg Centre where these pressures certainly were manifest in the attitudes and demeanour of the staff and, importantly, in some of the deficiencies recorded at audit.

5.4 COMPUTER SYSTEMS

Clearly, the lack of an effective, fully integrated computer system was a major concern. Indeed, to compensate for this deficiency, Centres had developed very complex systems that required multiple (and often excessive) transcription of results often including those that had already been interpreted and recorded by automated equipment. To assure the security of such systems, each Centre had devised its own system of complex checks (double/triple!) and balances.

Against this background it was considered imperative that firm assurances should be gained that "CISCO" was definitely on schedule. Nevertheless, there was concern that the Winnipeg Centre was amongst those who were not scheduled to receive/implement CISCO until the end of 1996. Whilst it is assumed that this process is in control, through the "offices" established by this process, the auditors would wish to enquire whether:

- . consideration has been given to establishing a "CISCO Training Centre" and implementing the system Nationally by a stepwise ie modular process.
- . contingencies have been made to introduce base laboratory systems if the implementation schedule slips.
- . consideration has been given to how inter-Centre transfers/issues for fractionation etc will work in a mixed system (computerised & manual).
- . consideration has been given on the extent to which BoB should be involved

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in this process (especially against the background of the excessive delay caused by their involvement in the validation of on-line printing of labels for source plasma).

5.5 FINANCE

Overall, there was concern that lack of finance was preventing GMP compliance eg throughout, blood component processing facilities fell below the standards required. In addition, cleaning and general building maintenance arrangements did not meet the standards required for GMP.

More specifically, whilst the Montreal Centre was reasonably well maintained, it was operating on 4 discrete sites and the layout was not conducive to GMP principles. There was no clean room or even "clean area" in which to undertake processing. This latter point was relevant in all 3 sites.

In Saint John, there was much equipment beyond its replacement date eg the BG15 blood grouping system and most chest freezers, whilst in Winnipeg the premises were considered inadequate in terms of their overall safety and suitability for GMP compliance.

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H Starr

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COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT
OF MONTREAL CENTRE
17 - 21 OCTOBER 1994

GENERAL SUMMARY

From the outset it was clear that the Regional Director has quite excellent leadership qualities and has assembled a very strong, very able and well focused management team. Throughout the Centre there was evidence that much effort had been expended to raise the profile, extent and implementation of Good Manufacturing Practices. There was evidence that these efforts were successful although, as might be expected in such a major undertaking, some areas have made more progress than others.

Numerous excellent systems were observed and although a number of important GMP deficiencies were reported, the auditors formed a very clear impression that the systems in place in the Montreal Centre were secure and, in some cases, represented a standard of practice that was as good the auditors had experienced anywhere.

Throughout, the auditees conducted themselves in a highly professional manner and their patience, co-operation and eagerness to help did much to facilitate the audit process. The auditors would like to express their appreciation for the assistance given. However, the extent to which the French language was used came as something of a surprise to the auditors and demanded an even greater than normal level of care and concentration throughout the process.

Whilst we are content that the inspection of the Montreal Centre was very thorough and in-line with practices elsewhere, it is important to emphasize that our report can only be based on those activities which were viewed and discussed during the inspection process.

A number of GMP deficiencies were identified and, to help the Montreal Centre resolve these, they have been ordered into groups. The most important deficiencies are reported as "Principal Matters of Concern" or "Other Major Matters of Concern" and are shown in detail in appendix 1. Those deficiencies of lesser impact are reported as "Other Points of Concern" and are shown in detail in appendix 2. The principal reason for recording all of those items in appendix 2 was to provide a record of every conceivable improvement opportunity.

Eight non compliances were classified as "Principal Matters of Concern" and there were six "Other Major Matters of Concern". These numbers, and the extent to which they might impact on the overall Service are not atypical of what might be expected from this type of GMP audit from a Centre that is striving to embrace the concept of GMP. However, the extent to which National policy and procedures feature in these 14 GMP non-compliances is worthy of note.

The completed checklist is attached as appendix 3.

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT OF MONTREAL CENTRE

17 - 21 OCTOBER 1994

APPENDIX 1

PRINCIPAL AND OTHER MAJOR MATTERS OF CONCERN

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL INSPECTION TEAM: AUDIT OF MONTREAL CENTRE
17 -21 OCTOBER 1994

PRINCIPAL MATTERS OF CONCERN

1.1 ARRANGEMENTS FOR PREPARING FROZEN/THAWED AND WASHED RED CELLS

- 1.1.1 Frozen red cells are prepared infrequently but about 10 units of washed red cells are prepared each day. OPEN PROCESSES ARE USED.
- 1.1.2 The area in which these processes take place was in a corner of an open laboratory. The area was very cramped - there was no free bench space, and the area was not suited to this activity. A ceiling tile above and behind the processing area was broken.
- 1.1.3 Connection of wash packs, red cells, addition of glycerol etc, takes place in this open environment, hands were not washed, gloves were not worn, no alcohol wipes, sprays etc were used.
- 1.1.4 The SOP for this procedure was a working draft that was prepared in October 1990 (LS 104 PSA 3.1) which contains multiple appended corrections and loose, handwritten sections.
- 1.1.5 The waterbath in the area was not monitored for microbiological contamination, although there was a label indicating that a "microbiologicide" was added on 12.09.94. It was stated that this should be changed monthly - the date of inspection was 19.10.94.
- 1.1.6 The SOP for freezing of red cells (CON; INS; 002; version 01; 14 Jan 1994) contained multiple, unauthorised handwritten changes.
- 1.1.7 The same problems as were described for the preparation of washed red cells also apply here, although there would be two opportunities for contamination (at freezing and at thawing).
- 1.1.8 Consideration should be given to increasing the security of the procedures used to label the packs of washed red cells and frozen thawed red cells.
- 1.1.9 No archive serum samples were being collected or stored for frozen red cells.

COMMENT: A review of sterility test data for these products showed no evidence to suggest that bacterial contamination was a problem.

It is recommended that these procedures (above) are reviewed as a matter of urgency to bring them into compliance with GMP.

1.2 SOPs FROM NATIONAL

- 1.2.1 The issue of National SOPs were seen to complicate and delay the development of effective local SOPs to implement National policy. It was stated that subsequent to the issue of National SOPs, memos could be issued by National that were to be included in/attached to the local SOP. The position in Montreal (and presumably in other French speaking areas) was further complicated by the need to wait for appropriate French translations of documents.

Having to refer to multiple documents was thought by the auditors to be unnecessary, unwieldy and did not facilitate the GMP process.

- 1.2.2 Of the National SOPs reviewed by the auditors, a number were considered not to provide clear, unambiguous instructions and some carried too little detail eg see #1.5, 1.10 and 1.11 in this appendix.

Others carried information that apparently was not being complied with (even by National) and there was no evidence that a National document review process was in place eg see #1.3 in this appendix.

COMMENT: It is recommended that National should only issue SOPs when appropriate and that such SOPs should contain sufficient detail for them to be used without change at local Centres. Policy statements need not be issued as SOPs.

1.3 PROCEDURES FOR PRODUCT WITHDRAWAL AND RECALL

- 1.3.1 This procedure was governed by an SOP from National - QA: 41: 24 August 1989. This SOP lacked sufficient detail and required the use of E-Mail which has never been used in this application by National (as far as Montreal Centre were aware) or in the Montreal Centre. The SOP has been unchanged since 1989.

- 1.3.2 There were no arrangements/procedures in place in the Montreal Centre to deal with fractionated product recalls or other problems out of normal working hours.

1.4 BLIS

- 1.4.1 The BLIS donor database software is maintained by National and they undertake all validation and change control.

The "users manual" issued by national was described as a "programmer's guide" and of little use to hands-on users of the system. To their credit, the local IT team have developed an excellent users manual for in-house use.

- 1.4.2 All donor information is keyboard entered ie there is no barcode entry of data. This is a major breach in the donor/donation positive identification loop. Nevertheless, internal checks and balances did seem to provide a secure system.
- 1.4.3 It was stated that the production of duplicate donor records was not difficult to do since the system does not use a phonetic check or other modern approaches. Staff vigilance and a monthly check minimise the scale of this problem.
- 1.4.4 In July 1993, the BLIS system "developed" a virus that required the user password to be changed at each log-on - this was previously required every two months. (BLIS has no virus check software). Subsequently, National have modified the programme to remove the need for password changes (and therefore security control). Nevertheless, as described it seemed that this did not pose a real threat to the security of the system at this site.
- 1.4.5 Of the various data transactions on BLIS only those concerned with input of Rh results, repeat reactive virology results and donation:donor linking were said to be audit traceable.
- 1.4.6 The BLIS system prints worksheets (L592/93 and L593/93) that have the check digit and last three digits shown unless the number is the first in the sequence or ends in -0 or -9 in which case the entire number is printed.
- 1.4.7 There was no documented procedure for reporting problems with BLIS. However, there is a hotline at National where problems are handled.
- 1.4.8 The Centre have made disaster recovery arrangements locally and with National but have not had approval to proceed with a live test.

1.5 TRANSCRIPTION

- 1.5.1 The transcription process has been designed to comply with National SOP QC7000; Ver 02; effective 30 June 1993 - Routine release of blood components and must use a worksheet that is also defined by National (L592/93 or L593/93 - French version).

The process was considered to be complex and requires the manual transcription of thousands of test results daily, even although almost all results have been generated by computerised reading equipment and are available as a hard copy. Whilst transcription procedures seem secure and involve independent checking by two persons, there is concern at the amount of transcription required and that it takes place in a fairly busy, open work area - with a radio on.

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- 1.5.2 The rate at which transcription errors pass both operators was said to be in the region of 3 per year or approximately one per million transcribed results. This was said to represent a significant improvement over the system it replaced.

It was not known how often the second operator detects/corrects errors in results, transcribed by operator 1 as the information was not being collected.

1.6 FINAL CONTROL

- 1.6.1 Whilst this final checking process was considered secure, a number of observations were made that provide opportunities to enhance security.

- 1.6.2 During inspection on 19 October 1994, it was noted that conforming and non conforming products were brought into the room at the same time. It would be better practice to dispose of non conforming product before taking "conforming" products into the room.

- 1.6.3 It was noted that during the final control of a batch of platelets, the products were brought into the room in a cardboard box and that the workflow went from left to right and back to left, into the same box. There was no reconciliation of what went into the room with ultimate fate.

It is recommended that the workflow should be in one direction only and that a reconciliation step is added to ensure that product discarded, placed in a hold condition and released to stock can be accounted for.

- 1.6.4 There is currently no requirement to document the reason for discard. This will be covered by a new procedure to take effect Monday 24 October 1994.

1.7 ATTACHMENT OF ABO BLOOD GROUP LABELS AT SESSIONS/INCORPORATION OF THE GROUP IN THE UNIQUE DONATION IDENTIFIER

- 1.7.1 The donor database requires the blood group as part of the unique donation number and, therefore, new donors and donors without cards are grouped on session (anti-A and anti-B) and are given a donation number that incorporates the blood group.

- 1.7.2 Primary and some satellite packs are labelled with an ABO blood group label at the session. This is not acceptable practice but it is understood that change will be implemented with the anticipated CISCO computer system.

- 1.7.3 The problem of misgrouping was said to almost always result from errors in grouping at sessions and was said to occur about 10 times per month. The procedures required to correct such errors are complex and time consuming and as such must give cause for concern.

*Martin Bury
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1.8 GOOD LABORATORY PRACTICE

- 1.8.1 There was a general lack of GLP in the laboratory areas. This can be illustrated with a few examples from the virology laboratory.
- 1.8.2 Donor samples were left uncapped on benches for long periods of time - the laboratory was very cramped and trays of samples could easily be knocked over.
- 1.8.3 Samples for repeat testing were placed into specific fridges eg HBsAg, however the racks were not labelled.
- 1.8.4 The expiry date of the conjugate was not marked on the bottle after its preparation.
- 1.8.5 The saline wash container for Hamilton AT sampler #B was not labelled to indicate the identity, lot number or expiry date of the contents.
- 1.8.6 Waste containers were not status labelled during the decontamination process.
- 1.8.7 Some equipment calibration records were missing.
- 1.8.8 Some unauthorised instructional notes were displayed.

OTHER MAJOR MATTERS OF CONCERN

1.9 GENERAL MANUFACTURING RECORDS/VALIDATION OF PLASMA FREEZING AND THAWING (FOR CRYO)

- 1.9.1 Blast freezer #RC-17A was used to freeze plasma for fractionation, clinical use and cryo production. Up to about 200 plasmas could be in the freezer at any one time. The standard freezing time was one hour, however, this process had never been validated to confirm satisfactory performance with a maximum load.
- 1.9.2 Plasmas were not frozen in discrete batches and there were no records of the freezing process eg contents of the freezing run; chamber temperature before starting; a chart of the temperature profile during freezing; start/stop times; operator identity etc.
- 1.9.3 Comments made above (1.9.1 & 1.9.2) apply equally to the Instacool freezer and the cryo thawing bath.

1.10 PREPARATION OF REPEAT REACTIVE SAMPLES TO SEND TO NATIONAL

Preparation of repeat reactive samples to send to National was covered by a National SOP (SL:121) but the procedure is not sufficiently explicit/detailed. Such

samples are decanted by one person into a tube that normally was said to be labelled by marker pen. Subsequent double checking of clerical details by another section does not check the decanting process.

1.11 DONOR IDENTIFICATION PRE VENEPUNCTURE

This is a requirement of the National SOP but the procedure is not sufficiently explicit and may also have lost some meaning in the translation to French. At the static clinic on 18 October 1994, the nurse escorted a donor to the couch and said "Good day Mr how are you today?"

This is not positive identification of the donor which should require the donor being asked to give their name and, at least, date of birth.

1.12 DELAYS IN SUBMITTING AUDIT RESPONSES

Whilst acknowledging current preoccupations within the Canadian Blood System it was thought that arrangements for dealing with matters of concern raised during audits by external agencies were less than optimal ie

- . Montreal received notification of a number of deficiencies raised by the BoB at their post audit meeting on 02 February 1994.
- . Montreal sent their response (to the matters of concern raised by the BoB) to National on 21 February 1994.
- . Montreal received a letter from BoB on 29 July 1994 confirming the matters or concern they reported during the post audit meeting in Montreal on 02 February 1994.
- . National communicated Montreal's response to the inspection during September 1994.

1.13 ABO AND RhD GROUPING OF NEW DONORS

Whilst not a requirement in Canada, there was concern that the ABO and RhD group of new donors was tested only once. This was true for donation samples tested on the Olympus PK7100 and for those tested manually.

1.14 WATERBATH FOR THAWING CRYO

The waterbath used to thaw cryo was said not to contain a bactericide and the water was said to be changed weekly. There was no log for the cleaning/water change routine and the water was not monitored for bacterial contamination.

1.15 UNIQUE DONATION NUMBERS

- 1.15.1 A set of donation numbers are stuck onto the reverse side of the primary blood pack

at collection. A smaller number are stuck onto the reverse side of the plasma transfer pack.

These numbers are used at various points during the manufacturing process to record donation numbers on worksheets, to produce a donation number for the washed red cell packs and so on. They are also used by hospital blood banks.

- 1.15.2 There is no record of the usage of these numbers and the entire set can be peeled off the pack without difficulty. In GMP terms, reconciliation of labels is fundamental and the ideal would be to destroy any surplus labels at collection.

This does not seem an option at the present time as it would require a substantial and widespread change to current practice. Nevertheless, it has been recorded so that it can be considered for future development.

- re 2.27.7 Subsequently to questions raised at the inspection concerning the +1°C lower storage limit for whole blood and red cells, as far as the auditors can establish the Canadian Drugs Directorate Guidelines 1992 specify a storage temperature of +2°C to +6°C. +1°C to +6°C is a USFDA specification. (The lower temperature limit specified by WHO; ATGA; UK and EC is +2°C).

*Martin Bruce
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COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT OF MONTREAL CENTRE
17 - 21 OCTOBER 1994

APPENDIX 2
OTHER MATTERS OF CONCERN

*Martin Bucci
Helmut Rahr*

2. OTHER POINTS OF CONCERN

<u>REF</u>	<u>AREA</u>	<u>DESCRIPTION OF PROBLEM</u>
2.1	Virology	System to reconcile samples received for testing with donations collected is reasonably secure - sometimes the information on samples/received from IT needs to be checked. (There is no SOP/documentation for this process).
2.2	Virology	Samples are centrifuged with their tops on. Tops are then removed and the sample tubes are held at +4°C overnight. There is no SOP for this procedure. It is recommended that this is given careful consideration as carry over could be a problem if more than one cap is removed simultaneously.
2.3	Virology	Fridges and freezers are not adequately status labelled and there is no inventory of contents.
2.4	Virology	Procedures for transferring and identifying manufacturers controls could be more secure.
2.5	Virology	Do not date the expiry date of conjugate on preparation - this is not covered in the SOP.
2.6	Virology	Records of calibration of Biotek EL312e reader are not numbered to link them to a particular calibration event. The summary page for the calibration record was missing.
2.7	Virology	Washers were subjected to a 3 monthly cleaning schedule with HCl/NaOH. Washer #82067 - cleaning record on 16 May 1994, may have been out of service but no cleaning recorded Aug 94 - explanation not given.
2.8	Blood Grouping	There were no manufacturing records for dilution of antisera eg batch of diluent (which must itself have a lot number); who prepared; who labelled; when this took place; pre release testing etc. There were no records of dispensing reagent red cells for antibody screening (as above).
2.9	Blood Grouping	Procedures for reading indirect antiglobulin antibody screening tests are not available as an SOP - a draft SOP was said to be under review.

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Alan Barr

- 2.10 **Static Clinic** Opened packs are held on the Central table until required. Manufacturer (Miles) recommends 30 days shelf life after opening foil pouch if resealed in pouch. Packs at clinic did not seem to be returned to foil pouch. Suggest this is reviewed.
- 2.11 **Static Clinic** No validation of arm (venepuncture site) preparation.
- 2.12 **Static Clinic** Sample for Hb estimation was collected over the paperwork.
- 2.13 **Static Clinic** Some of the maintenance records in apheresis were not complete but no action/comment had been recorded.
- 2.14 **Static Clinic** Staff indicated that there was an annual medical review of apheresis donors but no such records could be shown for a donor who had donated regularly over three years.
- 2.15 **Static Clinic** The senior nurse was unsure of the location of the ambubag. The drug box was checked and contained 3 vials of calcium gluconate that expired in January 1994 (lot # (L) 50-181-NJ).
- 2.16 **Transcription** Some of the worksheets used in this process eg figures 14 and 18, could be enhanced by the addition of a checking signature for completed sheets. This applies equally to other areas/activities of the Centre.
- 2.17 **Transcription** It is not acceptable to make pencil entries that are overwritten/changed. All entries to documents must be shown clearly.
- 2.18 **Components Lab** The transport form received in the components laboratory on 19.10.94 (approx 1.20pm) from session "VAP" was not completely fully ie # vehicle _____ temperature _____ were blank.
- 2.19 **Components Lab** Centrifuges were cleaned weekly but instruments #5A and #5B "had been cleaned" but not logged on 14.10.94 "because the individual concerned was part-time".
- 2.20 **Components Lab** Platelets were left to rest on the bench (sometimes in boxes) in an uncontrolled environment.
- 2.21 **QA** Excellent document and change control procedures were in place. The following minor points were noted:
1. some recalled (ie superseded) documents were not

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returned quickly enough, this should be covered by a tighter procedure.

eg one document recall request had been issued on 23 June 1994 but a document was still outstanding.

2. There was no means of ensuring that authorised/controlled documents could not be copied eg the use of coloured paper, coloured stamps etc.
3. There was no defined document review procedure.

2.22 **QA**

Although there is good evidence of effective equipment/procedure validation it was accepted that this should be concluded by a summary report which indicates whether the equipment/procedure can be introduced for routine use, when that should take place and an authorising signature/s.

2.23 **Customer Services**

The fractionated product inventory is held on a computer data base and is checked manually each week. Discrepancies were said to be found but no record was being made of the discrepancy and subsequent change to the computer inventory.

2.24 **Training**

At the present time, training of laboratory personnel was in the process of being implemented. Full implementation of the excellent training plans shown in the Centre's Quality Manual should be pursued (scheduled for Nov 94).

2.25 **General Documentation**

The availability and standard of SOPs varied substantially throughout the Centre. The matter is clearly receiving much attention as there is evidence of new procedures being written. This effort must be sustained.

Some important SOPs were not available and there was evidence of incomplete documentation (referred to elsewhere in this report).

Frequently, SOPs were not available where they were required ie often were held in a single folder. Many were very detailed and not "user friendly".

Empty spaces on worksheets were not "corrected" to show that eg no tests had been done - by crosshatching for example. The use of pencil input which is subsequently overwritten is not acceptable - all records must be shown.

2.26 **General Premises**

1. The premises clearly are too small to support all the activities undertaken eg

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- there were fridges in corridors
- the blood irradiator was in a corridor
- open processing of blood components was being performed in a corner of an open laboratory
- the virology and blood grouping laboratories were very cramped

2. The floors in production areas need to be sealed and cleaned to a defined schedule. There is no coving at floor/wall/ceiling junctions - this makes cleaning difficult.
3. Fibre ceiling tiles were not appropriate - some were broken, most notably where open processing was being performed.
4. In storage areas, fluorescent lights were unprotected eg in the warehouse above paper records.
5. In the warehouse the quarantine area for blood packs was not clearly defined.
6. The warehouse was not temperature monitored - stock of blood packs held there.
7. Some benching had badly chipped formica, noticeably in the components lab, which could present sharp edges. This exposed underlying chipboard (ie bare wood).
8. Bare wood also was exposed in containers beside donor couches.
9. There were no handwash sinks in laboratory areas.

2.27 **General, Fridges
Freezers etc**

1. The rubber seal on the blast freezer door #RC-17A was cracked.
2. Fluorescent lighting in walk-in cold rooms and deep freeze rooms was unprotected.
3. There was no internal cleaning routine eg #RC-17A had ice on floor and, especially, on ceiling.
4. Temperature monitoring probes were unlabelled as were

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the containers in which they were inserted (if any).

5. The temperature record sheets had some omissions eg #RC-15A no first entry 11.10.94; some had month and year; some had month only; some had neither. This would make tracking of records difficult.
6. The scale on some charts made reading difficult eg one division = 5°C.
7. It was considered that alarms could not be demonstrated to be activating at the temperatures stated eg +1°C; +20°C and -20°C and was considered that alarm checks could be carried out more frequently.
8. Those fridges which contained known biohazard material should be appropriately status labelled.
9. Storage areas should be locked to prevent unauthorised access.

Martin Bruce
Julian Rane

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT OF MONTREAL CENTRE

17 - 21 OCTOBER 1994

APPENDIX 3

INTERNATIONAL CHECKLIST

Martin Byce
Helena Rana

**COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA:
INTERNATIONAL AUDIT TEAM CRITICAL CONTROL POINT CHECKLIST**

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
1. DONOR SELECTION				
1. Is there an effective donor deferral procedure	UK; CDD; USFDA	✓		1.1.1. This includes a procedure for self exclusion.
2. Is there a register of donors with a history of repeat reactivity in mandatory microbiological screening tests?	USFDA; UK	✓		1.1.2. This is kept on microfiche and is updated monthly.
2 Do donor assessment areas provide an adequate level of privacy? ie can waiting donors see the completed questionnaire or overhear verbal questions and answers?	CRCS; UK; ATGA; CRCS; WHO; USFDA; CDD	✓		1.2. Excellent arrangements at the static clinic - mobile clinics not inspected.
3 Are prospective donors provided with information on AIDS/high risk activities at each donation?	USFDA; UK; ATGA; CRCS; EC	✓		1.5. Credit card size of information "leaflet" is given to every donor.
4 Do donors acknowledge in writing at each donation that they have read and understood the "health check"/"fit to donate" criteria?	USFDA; UK	✓		2.3.2. Will be making arrangements to validate the process
5 Are donors made aware that recipients experience risk from transfusion and are they, therefore, asked to report any illness developing subsequent to the donation?	UK; ATGA; CRCS; CDD	✓		3.1. Not adequate. National SOP requires donor identification before venepuncture but local interpretation is to say "Hello Mr _____ How are you today"
2. PREPARATION FOR VENESECTION				
1 Are blood packs inspected before use to ensure they are: 1. in date?	EC ATGA; UK	✓		3.3. System in the static clinic seems secure but apparently one nurse can be attending to 4 donors - this should be reviewed on busy mobile sessions to ensure the process is secure.
2. free from defects?	ATGA; UK; EC	✓		
2 Is there a secure procedure to ensure that donor records, blood packs and sample tubes are correctly labelled at the time of donation?	UK; USFDA; EC; CRCS	✓		
3 Is the procedure for arm preparation: 1. appropriate?	USFDA; UK; EC; ATGA; WHO; CDD	✓		
2. validated?			✓	
3. BLOOD COLLECTION				
1 Is the identity of the donor checked before venepuncture?	ATGA; EC; UK		✓	
2 If local anaesthetic is used, do the procedures for preparation and injection: 1. follow 'clean' procedures (aseptic)?	ATGA, EC	N/A		
2. explicitly exclude resheathing of needles?		N/A		
3. avoid any chance of donor/donor cross infection?	ATGA	N/A		
3 Are the donor attendant duties organised so as to prevent any mix up in documentation, samples or labelling between donors/donations?		✓		
4 Is the donation number checked on all items to ensure that those on the blood packs and sample tubes are identical with those on the paper work?	EC; UK	✓		

COMMENTS - IDENTIFY BY NUMBER

N/A - Not applicable

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Are any excess labels defaced/destroyed immediately after labelling is complete?			✓	3.5. Multiple copies of the unique donation are returned to the Centre and used in various applications.
6 Once the donation is complete is there a procedure that requires the container, samples and documentation, especially labels, to be checked for defects?	EC; USFDA	✓		
7 Adverse Donor Events 1. Is there a written procedure for resuscitation?	WHO; CDD	✓		
2. Are staff trained and annually updated in resuscitation techniques?	WHO	✓		3.7.1. There is a memo but not an SOP.
3. Is there a written procedure that requires the components of the resuscitation "kit" to be checked on a regular schedule and logged?			✓	3.7.3. 3 bottles of calcium gluconate were found to be expired (lot # (L) 50-181-NJ, exp 1/94)
4. TRANSFUSION MICROBIOLOGY				
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA		✓	4.1. Procedure is reasonably secure but is not written.
2 Are tests performed on samples taken at the time of donation?	WHO; USFDA; CDD	✓		4.4. Positive sample i.D. is lost when decanting samples into the marker pen labelled tubes for confirmatory tests.
3 Are reagents used as recommended by the manufacturer?	USFDA; UK; CDD	✓		
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA	✓		4.5. Check digit must be entered.
5 Is there a secure system for keyboard entry of numbers?		✓		4.7. Samples from National are used to pre-release test each new lot of kits.
6 Are samples ever manually added to test wells? If yes, describe the circumstances and procedures.		✓		
7 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes: manufacturers? in-house? licensing/national authority? how frequently tested?	UK; ATGA; USFDA; EC	✓ ✓ ✓ ✓		
8 Is a system of positive reporting used? (ie are results recorded for all samples)	UK	✓		
9 1. If results are interpreted by computer software, is this validated?	CRCS; UK	✓		
2. If results are interpreted manually, is this governed by a written procedure?	UK	✓		
10 For initial screening test positives and previously recorded positives, is there a secure procedure for ensuring that the correct samples are retrieved for repeat testing?	UK	✓		
11 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS	✓		
12 Are there secure, written procedures that permit the identification of all subcomponents of a donation and ensure their retrieval, disinfection and disposal?	UK; CRCS; USFDA; WHO	✓		

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
13 For components in long term storage, is there a secure procedure for storage, retrieval, testing and reporting of archive samples?			✓	4.13. Archive samples are no longer retained.
14 Are test data reviewed by personnel before final results are reported?	USFDA; UK	✓		4.16. There is a written procedure but this does not include double checking of the labelling / sampling procedure.
15 Do repeat reactive results produce a rapid deferral flag in the donor record?	UK	✓		
16 If confirmatory testing of positives is performed off site, is there a secure, written procedure for preparing and labelling samples?		✓		5.1 Procedure seems reasonably secure but is not written.
17 Is there a secure, written procedure for inputting and editing donor files on receipt of confirmatory test results.		✓		
18 For HBsAg and anti-HIV 1 + 2 repeat reactives, is there a written procedure to ensure that any previously prepared component still held in inventory is quarantined?	USFDA		✓	5.3. Antisera reagents are diluted but there is no check / record of the dilution process.
5. BLOOD GROUPING (ABO & RhD)				
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA	✓		5.4. For manual blood grouping, samples are given a sample reference number to link them to the donation number but - seems OK.
2 Are tests performed on samples taken at the time of donation?	USFDA; WHO	✓		
3 Are reagents used as recommended by the manufacturer?	USFDA		✓	5.5. Requires check digit but not double entry.
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA		✓	5.6. Control red cells are used for ABO and Rh.D grouping, they are obtained from whole blood donations and are tested at the beginning and end of each series of samples (up to 500)
5 Is there a secure system for keyboard entry of numbers?		✓		
6 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes, describe: controls used their source how frequently tested	UK; ATGA; USFDA	✓		5.7.2. There are no written procedures for manual antibody screening of donor samples.
7 1 If results are interpreted by computer software, is this validated?	CRCS	✓		
2 If results are interpreted manually, is this governed by a written procedure?		✓	✓	
8 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS	✓		
9 Are test data reviewed by personnel before final results are reported?	USFDA; UK	✓		
6. COMPONENT PREPARATION				
1 Is there a procedure that ensures a rapid and effective reconciliation of all components at all stages of their manufacture?		✓		6.1. There is a procedure but it involves checking various worksheets / records.

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
2 If an open processing system is used; 1. is component sterility testing performed?	UK	✓		6.2 BUT OPEN PROCESSING IS A MAJOR PROBLEM.
2. is environmental monitoring performed, especially during the open procedure?	UK		✓	6.3.2. CONTINUAL VALIDATION AS PART OF ROUTINE COMPONENT QC.
3 If a sterile connecting device is used 1. is the system validated?	UK	✓		6.4. BUT PROCEDURE IS A POORLY DEFINED DRAFT. RELABELLING PROCEDURE COULD BE MORE SECURE.
2. what is the validation interval?				
4 Where component preparation requires relabelling of a pack eg for washed red cells or for pooled platelets 1. is this governed by a written procedure?	UK	✓		7.1 SECURE, BUT INVOLVES AN EXCESSIVE AMOUNT OF MANUAL TRANSCRIPTION.
2. is the procedure secure?	UK		✓	7.3 PROCEDURE WAS LAST USED IN JULY '93 FOR LEUCOCYTES (APHERESIS)
7. COMPONENT LABELLING & RELEASE TO STOCK				7.4. National SOP QA: 293 25 Aug 1989.
1 Do procedures ensure that components cannot be released to stock until all the required tests (mandatory and additional) have been completed, and records reviewed, with satisfactory outcomes?	UK; USFDA	✓		
2 Is the procedure for labelling blood components? 1. a written procedure	USFDA	✓		8.1.3. Components that are repeat reactive are not placed in "biohazard" storage until confirmed. Frozen components are not removed until the session is "called."
2. secure?		✓		
3. followed?		✓		
3 In exceptional instances are components issued when they do not conform to mandatory requirements (eg test results not available). If yes, is this governed by a written, secure procedure?	UK; USFDA	✓		8.2. Concerned that the lower limit for 4°C storage was said to be +1°C.
4 Are blood components ever received from non-Red Cross blood collection facilities? If yes, is this covered by a written, secure procedure?	CRCS	✓		8.3. Validation only annual at present.
8. COMPONENT STORAGE				
1 Do blood component storage areas and procedures allow for appropriate segregation and effective identification of components of different status eg 1. untested	UK; CRCS EC; USFDA; CDD	✓		
2. "hold" status		✓		
3. Biohazard			✓	
4. available for issue		✓		
2 Are arrangements for monitoring the temperature of blood component storage areas adequate?	CRCS; UK; CDD	✓		
3 Are monitoring systems and alarms regularly validated to ensure functionality.	EC; UK	✓		

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
9. INFORMATION TECHNOLOGY				9.1 Source code for BLIS is held at National. They undertake all validation / change control etc.
1 Has the computer system been validated to provide assurance that the system operates properly in the intended environment? If yes, is this documented?	USFDA; ATGA USFDA	✓ ✓		9.3 In-house user's manual produced. Manual from National of use only to 'programmers'.
Are all changes and modifications that are made to the computer system evaluated to assure that no other areas of the system are adversely affected by the change?	USFDA; CDD	✓		
2 Did the validation reflect normal, stress, exceptional, boundary and invalid conditions?	USFDA	N/A		9.4 Training is mostly given to I.T. staff.
3 Is the computer system covered by an appropriate users manual?	CRCS; ATGA; EC; USFDA; CDD	✓		9.5 Due to problems with a computer virus, BLIS is not password controlled.
4 Are users of the system given adequate training?	CRCS; USFDA	✓		9.6 Only input of Rh group, repeat reactive virology result and donor: donation linking are audit traceable.
5 Does the system have security procedures to prevent unauthorised access?	USFDA; ATGA; CDD; CRCS; EC		✓	9.7 Problems are reported to National via a 'hotline' - there is no written procedure.
6 Is an audit trail maintained so that all changes made to the data can be traced?	ATGA; USFDA		✓	9.8 Programme can only be changed by National.
7 Is there a procedure for reporting problems with the system?	USFDA; CRCS	✓		9.9 Have established a disaster recovery plan - use National PDP11 + local backup but have not been allowed a live test.
8 Are written change control procedures available and effective?	USFDA; ATGA; EC	✓		
9 Are there recovery procedures to return the system to its previously operating state without loss of function, reliability, data or memory?	ATGA; EC	✓		10.2 Reasonable systems exist at present but a detailed training plan is due to be implemented in Nov 1994.
10 Is barcode quality/readability monitored?			✓	11.3 Need to introduce a mechanism to prevent copying.
10. TRAINING				
1 Do employees have appropriate education, training and experience?	USFDA; EC; CRCS; WHO; UK; CDD	✓		
2 Does the training programme include an annual performance review and identification of training needs?	CRCS; CDD	✓		
3 Is employee training documented?	CRCS; UK; CDD	✓		
11. QUALITY ASSURANCE				
1 Is there an individual responsible to management for quality who is independent of production/manufacturing?		✓		
2 Does this individual have sufficient authority to function effectively?	EC, ATGA	✓		
3 Is there a system to control the review, issue, use, retrieval and storage of documents?	UK; CDD	✓		
4 Is there a programme of self inspections (audits).	EC, UK; CDD	✓		

COMMENTS - IDENTIFY BY NUMBER

11.4. There have been 3 inspections this year and a programme of inspections will be implemented from November 1994

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Is there a procedure to ensure that new equipment, tests or procedures are validated 1. before being introduced for routine use?	EC CDD	✓		11.5.4. This has been noted and will be actioned.
2. After repairs or readjustments which may affect performance.				11.6.2. These are separate procedures.
3. If any problems are suspected.				
4. Does the procedure include the production of a validation report that indicates authorisation is given to introduce (or not) this new piece of equipment/test/procedure, the date of authorisation and the date of introduction?			✓	11.7. Sol from National has not been converted to a local procedure.
6 1. Is there an effective, written procedure/s for product recall?	UK	✓		11.8. Yes for fresh components,
2. Do the recall procedure/s apply to fresh blood components and fractionated products.		✓		No for fractionated components
3. How often has the procedure been used in the last 12 months for: blood components? fractionated products?		x 2		11.9. There was no GMP system approach to
7 Is there an effective, written procedure for reporting adverse reactions to fractionated products, blood components?	CDD; USFDA		✓	frozen/thawed/washed red cells. (open processing in a poor environment with poor procedures.
8 Is adequate provision made to support these adverse reaction/recall procedures out of normal working hours?		✓	✓	
9 Is there a consistent approach to GMP (across all component/product types and processes)?		yes	✓	

COMMENTS - IDENTIFY BY NUMBER

STRICTLY CONFIDENTIAL

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL INSPECTION TEAM: AUDIT OF SAINT JOHN NB
24 - 28 OCTOBER 1994

GENERAL SUMMARY

The Management Board at the Saint John Centre clearly work well together under the leadership of Dr McKay. Throughout, the Centre had some excellent systems and some quite excellent staff. Indeed, the general level of professionalism must be commended.

More recently the centre has been working very hard to develop an understanding of the concepts of Good Manufacturing Practices, to develop systems that comply with these concepts and to implement them across all activities. Although a number of GMP failures were recorded, there was evidence that good progress is being made and the auditors formed a very clear impression that the systems in place in the Saint John Centre were secure and effective.

Against this background of security, the deficiencies in GMP reported here-in should be viewed in the context of providing opportunities to build a GMP approach into and around the secure foundation.

Throughout this process, all staff contacted conducted themselves in a highly professional manner and their patience, co-operation and eagerness to help did much to facilitate the audit process. The auditors would like to express their sincere thanks for the assistance given.

The audit has been very thorough and has uncovered many areas in which GMP can be improved. It must, however, be appreciated that the number of non compliances raised in any particular area has more to do with the length of time spent in an area and the depth in which the audit was conducted than some notional association with safety/quality. Sometimes this link exists, sometimes it does not eg numerous minor non compliances were recorded in the TD laboratory. However, the standard of systems, documentation and records in that laboratory were of a very high order.

Of the GMP deficiencies identified, an effort has been made to classify them into "Principal Matters of Concern", "Other Major Matters of Concern" and "Other Points of Concern". The purpose of this clarification is to help the Saint John team focus on dealing with the major issues (the first two categories) whilst providing details of every conceivable improvement opportunity (the latter category). It must be stressed that many deficiencies in this latter category would not normally be formally documented by the auditors. (Responsibility for doing so would reside with the auditees). In this instance we considered it would be more helpful to list everything.

Ten non-compliances were classified as Principal Matters of Concern and a further ten were listed as Other Major Matters of Concern. These numbers, and the extent to which they impact on the security of the Service are not atypical of what might be expected from this type of GMP audit from a Centre that is striving to embrace and implement the concept of GMP. However, the extent to which National SOPs and policies feature in these GMP non compliances is worthy of note.

More detailed information of the non compliances are listed in appendices 1 and 2, the completed checklist is attached as appendix 3.

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL AUDIT TEAM: INSPECTION OF SAINT JOHN (NB) CENTRE

24 - 28 OCTOBER 1994

APPENDIX 1

PRINCIPAL AND OTHER MAJOR MATTERS OF CONCERN

*Marki Bucci
Helen Rann*

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL AUDIT TEAM: AUDIT OF SAINT JOHN NB

24 - 28 OCTOBER 1994

1. PRINCIPAL AND OTHER MAJOR MATTERS OF CONCERN

1.1 PRINCIPAL MATTERS OF CONCERN

- 1.1.1 Components
- > about 40% of the plasma expressors had badly corroded backplates with blistered surfaces.
 - > this was probably caused by the use of hypochlorite (Javex) as a cleaning agent.
 - > the blistering could have caused pinhole leaks in packs - (although there was no evidence of such a problem)

- 1.1.2 Blood Grouping
- The BG15 is now 20 years old. Although the Centre has no record of ever issuing components that were wrongly ABO grouped, the system does not allow positive sample identification. Serious problems were observed with the sequential numbering equipment eg on 25.10.94 the following were noted on the blotting paper printout.

101347	corrections were in
101346	ball point pen.
101345	For repeats, entire
1013454 ← Duplicate number printed	number was appended.
↑	
wrong number (4 instead of 1)	

It was acknowledged that the sequential printer #174/76 was causing problems but there was no log to quantify the scale of the defects or their frequency.

Lack of spare parts and secure arrangements for maintenance and support also were concerns.

1.1.3 Blood Collection

Occasionally at the checking table the operator would notice a transfer pack that had a missing blood group/donation number. The nurse responsible for the donation can be traced from available worksheets. The omission is communicated and the nurse searches through the waste container, locates the spare group/number label and attached it to the unlabelled pack. This was said to be more common on mobiles.

Martin Bruce
Allen Rarr

1.1.4 Controlled Temperature

Storage Areas

There was a problem with low temperature storage areas that was especially bad for frozen storage ie

- > the alarm system could not be shown to be working adequately
 - . there was no check (formally) that the after hours service contractor responded to an alarm event
 - . there was no COP to detail contingency plans for out of hours storage problems
 - . internal probes on the chest freezers were not accessible and therefore could not be checked for alarm or calibrated against a temperature standard
- > it was not known where the temperature probes were located in the chest freezers or how these were connected to the alarm system.
- > plasma boxes were stored to the top of the chest freezers but no mapping of storage temperature had been performed to confirm adequate temperature of product at the top of the freezer. Load limits had not been determined.
- > several freezers appeared to have a frost line halfway up indicating there may be a temperature problem with the upper half of those freezers.
- > on the advice of the service engineer, defrosting was no longer done to a regular schedule, only when "necessary" (about six monthly). Many had a build up of ice on the sides, sometimes reaching the lid. The lid lining also showed signs of ice underneath.
- > seals on most doors and lids needed to be replaced.
- > floor areas between and behind chest freezers was very dirty and floor tiles were raised and cracked. Water cooling system for the freezers fed into open drains on the floor.

1.1.5 General Management:

GMP

There was no adequate separation of Production and Quality Assurance duties and responsibilities. Although the position of QA Specialist is fairly new and continues to evolve, this individual had insufficient authority/responsibility to function as a QA Manager within a system of GMP.

1.1.6 Product Recall System

Recall of fractionated products is governed by a National SOP QA:41 (effective 24.08.94).

A recall of Factor IX (Immuno lot #050991035) was initiated by National on 17 Nov 1993.

- > This was not performed (by National) according to SOP QA:41, which indicates the Manager, Fractionation Products contacts Centres by phone and, within 6 hours by E-Mail. Contact Director and QA Manager.
- > This recall was sent by the National Medical Director to Centre Directors by fax - no telephone call or E-Mail was received in Saint John and the QA Manager was not contacted by National.
- > The faxed recall notification was sent to Saint John at 17.04, 17 Nov 1993 - this was 18.04 at Saint John and there were no staff in the office to receive the fax.
- > The faxed recall notification was received at 08.45 18 Nov 1993 and copied to the laboratory manager at 08.50am.
- > Saint John's response to this recall was excellent but was not covered by a COP.
- > There is no COP for the recall of fresh blood components.

1.1.7 National SOPs and Directives

There was abundant evidence that the issue of SOPs and directives from National were causing problems in Saint John eg:

- > the Centre is waiting on several National SOPs before they can produce and implement local COPs.
- > National advised they would be changing their document numbering system but the change is confusing and incomplete. Consequently, the Centre has devised an index system that refers to both numbers eg QA172 changed to CQ0001 in Sept 1992; some documents are still on the old system others are in the new system. From an audit point of view and for document control, this is not good practice eg SOP 517 version 2 has been superseded by TD:4000 version 1 but the new version does not refer to the original SOP.

This situation is further confused by memos from National notifying intended number changes eg NSG:100 to become BC1010 but the change has not taken place.

- > It was noted that National are planning a third number change to coincide with the provision of National SOPs in a new format.
- > Some National documents eg directives concerning changes to donor selection criteria, were issued without an implementation date and do not have controlled document reference numbers (eg National file ref #521:500:15 -

*Marki Bruce
Belin Rana*

issued 20 June 1994) - 5 days later a further update memo was issued in the same way for the same document. This seemed to be a recurrent situation.

- > Unreasonable demands were being made to implement multiple changes rapidly eg
 - . D94-044 version 1.0. National issued a directive on this new SOP NSG:140 (QC of CuSO₄) on 21 Sept 1994. (Note the apparently old number format - NSG was to become BC!)
- This was received in Saint John on 22 Sept 1994 and it required the Director to approve centre policies needed to effect this procedure and respond by 30 Sept 1994 to confirm receipt and compliance. (Saint John responded by 26 Sept 1994 but only because they had been piloting the procedure).
- . enforced change in Apheresis procedures from Baxter to Haemonetics. A phased implementation was announced Aug 1994, Saint John begins 31 Oct 94.
- > The authorisation page of National SOPs is not always completed accurately eg SOP NSG:100 dated 2.7.92 the "Prepared by" and "signed by" sections were not signed by the person named and the date against the Directors signature was 8.7.9.
- > National SOPs are not issued in a format that would prevent copying and there is no evidence that they are reviewed to a scheduled timescale.

1.1.8 Transcription Processes

Whilst the transcription processes viewed at Saint John were considered to be secure, there is concern at the amount of manual transcription, particularly of machine interpreted results, and of the numbers of checks and balances being used to give assurance that the system is in control.

1.1.9 BLIS

There were several points of concern relating to the BLIS system eg:

- > there was no adequate users manual. Such a document presently was being compiled in house - some aspects were incorporated within various COPs.
- > all information is keyboard entered - although this is initially input by lab staff and checked by computer services.
- > duplicate donor records can be produced.
- > there is no facility to enforce a regular change of password.
- > it seemed that RhD negative results were double checked on entry - all others were RhD positive by default. (No time to

Martin Bruce
Allen Rana

confirm this with laboratory personnel).

- > the full donation number is not printed on the L592/93 worksheet.
- > there is no adequately developed disaster recovery plan.

1.1.10 Unique Donation Identifier

The donor database requires the blood group as part of the unique donation number, therefore new donors/donors without cards must be grouped on session before a number can be allocated.

ABO blood group labels are attached at the time of collection ie before laboratory testing.

Approximately 2 (session/clinic) grouping errors were reported each month. The procedures required to correct these errors were complex and time consuming. Although it is understood that these are National problems, it is recommended that the blood group should not be part of the unique donation identifier and that the blood group should not be attached to the pack until after testing is complete.

1.2 OTHER MAJOR MATTERS OF CONCERN

1.2.1 TD Testing

Results of confirmatory TD tests for repeat reactives are input to BLIS by a charge technologist. The accuracy of this edit would not be checked until reviewed by the computer office staff which was thought took place on a monthly basis. It is recommended that editing of TD status is checked by a second person at the time of entering the information to the system.

1.2.2 Blood Collection

Procedures for identifying donors on clinics were not acceptable eg "Hello Mr _____, how are you today". Donors should be asked to give their name and, at least, date of birth.

1.2.3 Components

There were no validation data for either of the Instacool plasma freezers. There were no records of the freezing runs eg chamber temp before freezing; identity of person who loaded/unloaded; contents; start/stop times; temperature profile during freezing etc.

1.2.4 Components

There were no validation data or thawing/refreezing records for cryo production.

Water could be in the cryobath for up to 5 days - no bacteriological monitoring was performed and

Marki Bruce
Helena Ross

bacteriocides/bacteriostats were not added. Cryos were refrozen on dry ice.

1.2.5 Frozen/Washed Red Cells

These procedures are performed infrequently. A laminar flow cabinet is used for the "open" processes but clean technique is not used eg gloves are worn by are not sterile, connections are not sprayed with alcohol before being made; there were no records of cabinet use; settle plates were not used.

The COP for this process is not an official, controlled document and contains unauthorised written corrections. This document was written in 1986.

1.2.6 Red Cell Antibody Screening

The indirect antiglobulin phase of the antibody screen uses a pool of 5 sera tested at normal ionic strength vs a pool of 2 red cells.

- > the pools are prepared by taking 4 drops (by glass pipette) per sample. Tubes are not transferred to a new rack to avoid repeat sampling/mix up.
- > controls do not reflect the 1/5 test dilutions.
- > the results of pool tests are not recorded - individual results are transcribed onto the worksheet.
- > the procedure has not been adequately validated.

1.2.7 Unique Donation Numbers

A set of unique donation numbers are stuck onto the reverse side of the primary blood pack at collection. These numbers are used at various points during the manufacturing process (to stick onto packs, sample tubes, worksheets etc) but there is no control over their usage. In GMP terms, reconciliation of labels is fundamental and the ideal would be to destroy any surplus labels at collection (see also 1.1.3).

1.2.8 ABO/RhD Grouping of New Donors

Whilst not a requirement in Canada, there was concern that the ABO and RhD groups (D pos) of new donors was tested only once.

1.2.9 Health & Safety

There were a number of observations on health and safety matters that are recorded for information:

- > loose electric cables were observed on the floor in the donor clinic.
- > an electric cable was sellotaped across the floor in the TD lab.
- > the PVC covering of an electric cable on one of the Forma Scientific cryoaths was worn.

Martin Bruce
Kevin Rose

- > in the QC lab an electrical connection was noted behind a sink and beneath a towel dispenser.
- > there was a lack of sinks designed for handwash only and a perceived lack of handwashing.
- > the floor covering in the walk in deepfreeze was unsafe.
- > a centrifuge noted in the blood grouping laboratory did not have a lid lock (S/N 4287554).
- > blood irradiator was in an office.

Although omitted from this listing at the "wrap up" meeting on 28 Oct 1994, it was felt that failure to attach an expiry date to blood components was of major concern and should be noted in this confirmed final report.

Markin Byce
Allen Rana

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL AUDIT TEAM: INSPECTION OF SAINT JOHN NB CENTRE

24 - 28 OCTOBER 1994

APPENDIX 2

OTHER MATTERS OF CONCERN

Marki Buse
Helena Rana

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL INSPECTION TEAM: AUDIT OF SAINT JOHN NB
24 - 28 OCTOBER 1994

2. OTHER MATTERS OF CONCERN

<u>REF</u>	<u>AREA</u>	<u>DESCRIPTION OF PROBLEM</u>
2.1	Virology	<p>Service records for summit #1046.048 S/N were excellent and maintained in an orderly fashion but the required 3 monthly preventative maintenance schedule had not always been adhered to: eg</p> <p>25/03/93 next due date 25/06/93 - next done 10/08/93 10/08/93 next due date 10/11/93 - next done 04/01/94 There was no explanation for this in the log</p>
2.2	Virology	<p>Calibration of summit dispense volume - failure of pipette calibration was said to require a service visit. Double failures were logged on 07/02/94 and 21/02/94 but no service visits had been recorded. No appropriate explanation available in the records.</p>
2.3	Virology	<p>Forms being used were not incorporated into the controlled document system eg tdl equip; GABE1; tol volume.</p>
2.4	Virology	<p>Sodium chloride wash solution was prepared from aliquots of NaCl that had been preweighed and stored in unlabelled, stoppered tubes. There was no "batch manufacturing record" for this process eg lot # of NaCl; who weighed and added to tubes; who labelled (at least ID; lot number; expiry; storage temp) etc. There was no COP for the process.</p> <p>Similarly, there was no record for the preparation of 0.1N NaOH held in hood (? 107320X). This solution had been prepared on 30/11/92 but there was no record of expiry.</p>
2.5	Virology	<p>The hood in the HCV laboratory carried unauthorised, instructional notes eg procedure for sampling/dispensing the Ortho HCV assay. Such instructions should be part of the (COP) controlled document system.</p>
2.6	Virology	<p>With respect to records of calibration for the Cavro, until 02/08/94, the serial number of the Cavro being calibrated had been recorded on the calibration record sheet. This information does not appear in the</p>

Marki Buse
Helmut Rane

entries for 02 Aug; 06 & 15 Sept; 03 & 24 Oct - all 1994.

- 2.7 **Virology** There were no linearity or drift records for the microplate reader.
- 2.8 **Virology** With respect to checking microplate reader functionality with Methyl orange (TD 5000: version 4), the procedure was considered acceptable if there were "two outliers" - this practice is questionable since donor testing would require acceptable results in all wells. On 21/06/94 the OD check failed 3 times but there was no record of action taken.
- 2.9 **Virology** Acceptability of new lots of anti-HCV kits (Ortho) is based on tests with a panel of samples provided directly by the manufacturer (Ortho). Although these samples are also being tested by National, the validity of the approach must be questioned.
- 2.10 **Virology** The deepfreeze containing virology test kit lot validation samples and training panels was not biohazard status labelled, was not locked and contained multiple other reagents and samples. There was no inventory of contents (especially important for positive materials).
- 2.11 **Virology** There is no good segregation of new test kit lots from those tested and approved for use. On receipt of a new test kit lot, a laminated "on-test" type instruction is taped to the lid of the top box. Suitability for release is by exception ie if "on-test" label is not there, test kits can be used. This is not GMP.
- 2.12 **Virology** Operator identity is logged for each of the TD screening assays. However, if the operator changes during the test procedure this is not (always) recorded.
- 2.13 **Virology** 37°C incubators are used for the Sanofi HBsAg assays (3 in number). These have a digital temperature display but the actual temperature has never been validated nor calibrated against an independent temperature standard.
- 2.14 **Virology** The plate washers in the TD lab have unauthorised, undated instructional notes on top. Apparently, these were attached by the maintenance company. (It seemed that white-out had been used in the preparation of these notes) eg S/N 47772.
- 2.15 **Virology** Samples for repeat TD testing are held in the bottom section of a "split door" 4°C fridge (#C.19). The bottom door does not have a biohazard status label. There is no temperature logging/monitoring of either compartment of this fridge. The top section is for samples to be sent to National. Status labelling of these fridges would be helpful.

Martin Bruce
Alan Parr

The door seal was badly in need of attention.

- 2.16 **Blood Grouping** Reagent manufacturing records were not adequate eg:
- > with respect to antisera for the BG15, there was no record of the #lot no of saline; BSA; PVP etc used in the formulation. Each must be traceable.
 - > donation numbers of samples used for daily controls were recorded on the daily quality control form but not on the sample tubes (only the group was shown).
- 2.17 **Blood Grouping** On the L592/93 worksheet for the Saint John Centre clinic of 24/10/94, donation #A, [6] 252407, the reaction recorded for donor plasma vs A₁ cells had been changed from - to + but there was no initial to confirm the change was acceptable.
- 2.18 **Static Clinic** Some uncontrolled/unauthorised/undated instructional notes were seen in the blood collection area eg the "DO NOT DONATE" laminated leaflet; "ATTENTION FEMALE DONORS" leaflet.
- 2.19 **Static Clinic** There was no COP to describe the registration procedure available at the registration desk (was said to be incorporated within another department's COPs).
- 2.20 **Static Clinic** Prior to donation, donors held various loose records; registration form; donation numbers etc. It was thought that if this practice continues it would be safer to place all such items in a sealable plastic wallet.
- 2.21 **Static Clinic** There had been no validation of the arm cleaning technique.
- 2.22 **Static Clinic** Biohazardous waste was discarded into unmarked containers beside the bleeding couches.
- 2.23 **Static Clinic** There was no inventory of packs stored in the bleeding room (ie unused) and the storage area temperature was not monitored/logged.
- 2.24 **Static Clinic** Duration of bleed was not recorded, there was no written policy to define a slow bleed.
- 2.25 **Static Clinic** It was felt that all waste material from the donation process should remain at the bedside and that donors should not be asked to hold cotton wool against the VP site, subsequently to be discarded in the "common seating area".
- 2.26 **Static Clinic** The procedure for recording the lot number of harnesses, anticoagulant and pack should ensure that the records are taken from the actual

Martin Byrne
Helena Kane

packs etc and not from the "standard" lot no for that day.

- 2.27 **Static Clinic** No record of CPR training for physicians.
- 2.28 **Product Management** COP for anti-HCV ie INV:100:version 1, effective 10/02/94 did not contain the 'lookback/traceback/inventory tracking record' PM:011. (This was used for HCV but had been incorporated in all other TD COPs).
- 2.29 **Components** On receiving the clinic worksheet from clinics, components sometimes find numbers/samples/donations do not reconcile. These problems are investigated and resolved but no record of the incident is made ie treat the effect without establishing the cause!
- 2.30 **Components** Do not record check digits - transcription of numbers must be consistent throughout Centre.
- 2.31 **Components** Components are required to be returned for processing within specified temperature ranges. There is no checking of recorded transport temperature or subsequent authorisation to proceed (on the basis that the transport temperature was OK).
- 2.32 **Components** Component centrifugation profiles were taped onto the instruments - these 'aide memoirs' were not incorporated into the controlled document system eg they were undated, unauthorised, did not carry a COP ref number eg S/N 7193.
- 2.33 **Components** There were no acceptance/rejection criteria for speed/temperature checks on centrifuges (although it was good that these were being done). It could not be demonstrated that the service temperature checks undertaken by contract maintenance provided the necessary assurance that temperature was accurate eg could the equipment used to be traced to a standard?
- 2.34 **Components** Platelet concentrates were left to "rest" on flat cardboard boxes for 1½ hours. The environment was uncontrolled and there was no record of the "resting" process.
- 2.35 **Components** There was a requirement to log the temperature of the components lab 3 times daily and once on weekends, the acceptable range is 20°C - 24°C. The log for October 1994 showed.
- | | | |
|--------|--------------|-----------|
| 06 Oct | 4pm-4.30pm | no record |
| 23 Oct | 9pm - 10pm | no record |
| 02 Oct | 8.30am - 9am | 19.8° SM |
| 15 Oct | 8.30am - 9am | 19.1° SC |

Marki Buse
Helin Rann

16 Oct 8.30am - 9am 19.4° LC

No comments were entered to indicate these matters had received attention.

2.36 Components Cleaning schedules & "premises/fitments"

- > benches were wiped down daily with 1/10 Javex (hypochlorite) which was given a 1 week shelf life. No one could comment on the choice/efficacy of the dilution or the assigned shelf life.
- > centrifuges were cleaned weekly and this was logged. Cleaning also took place after bursts but no entry was made to the log.
- > tops of cupboards (wall mounted) in the components lab were extremely dirty (scheduled only for an annual clean).
- > floor areas behind centrifuges were extremely dirty - there was no cleaning record.
- > some ceiling tiles were damaged and there were chipped/loose formica facings on benches.
- > the door to the corridor was wedged open.

2.37 Components To facilitate the RP/RP15 boxing process, worksheets are not made up (ie boxes are not filled) in a group-specific manner. Internal procedures then require that the "techs" responsible for each TD assay check the suitability of each plasma donation from their group specific reports. This work is tedious and, it seems, unnecessary.

2.38 Components Until the check described in 2.37 is complete, boxes are held in the quarantine (untested) side of the walk-in freezer. The arrangements for separating tested and untested plasma boxes was considered inadequate. The storage arrangements were viewed.

Untested plasmas were held in numbered, opened boxes - plasma could easily be added to/switched between boxes. A pack was viewed # 570 6 494086 B. A red number appended to the bottom of the pack label indicated this plasma should be in box # 1003 - it was, in fact, in box # 1005. A number of plasmas were viewed and it appeared that plasmas destined for box #1003 had been placed in box #1005 and vice versa. It is a concern that this double error was not noted at initial boxing. The fractionation form (F040095 03/94) for box #1003 was viewed and confirmed that box should have contained #570 6 494086 B.

Whilst it was stated the error would have been noted at the final box checking stage (contents checked against the worksheet 1 box at a time) clearly this should not have occurred.

2.39 Components It seemed that between the final box checking process and placing in

Martin Bruce
John Harr

tested storage awaiting collection there was an unnecessary quarantine stage (in a chest freezer). Some of these boxes were taped shut, others had plastic sticking out to "help lift the boxes out of the freezer". This latter action might lead to excessive damage to plasma lines & ports on the frozen packs.

A label stating "Cleared for Fractionation" or similar, signed & dated would be helpful.

- 2.40 **Components** Boxes of plasma were stored on the floor and against the walls of both
Product walk-in and chest freezers contrary to the requirement for adequate
Management? circulation of air around the stored product.
- 2.41 **Components** Cleaning in all storage facilities was not good. Fans in the freezer
? Product room had icicles and because the tiled floor was very dangerous,
Management matting was laid (temporarily) to avoid slipping. This was dirty and
shed fibres readily. Several freezers had eg component labels,
quarantine labels, reagents, microplates and foil lying in the bottom.
- 2.42 **Product** Temperature monitoring probes in various rooms and pieces of
Management equipment should be suitably labelled. It would be helpful if they
were traceable to an index book eg #no; location; position; air/fluid
(type & vol); date calibrated, date calibration due etc.
- 2.43 **Product** The defrost cycle in the walk in freezer (#23) caused an unacceptable
Management perturbation in storage temperature (from -20°C to -40°C).
- 2.44 **Product** The high (too warm) alarm set point for the walk in freezer #23 was
Management said to be -20°C. The setting recorded on the "Refrigerator/Freezer
Alarm Guide - (guide/March 1994) indicated this set point was -10°C
ie the change had not gone through an effective, controlled process.
- 2.45 **Product** Autoclaving
Management > records for TD positive donations carried records of disposal
of specimens but did not indicate the number/type of
specimens.
> specimens were not retrieved and destroyed (or were not
recorded) for syphilis screen positives.
> it seemed biohazardous waste could be left for up to 7 days
before autoclaving - this seems too long eg the record for
autoclave bag #39 30/9/94 showed it contained a donation from
07 Oct 1994 (O 6 101120). The explanation given was that the
bag also would have contained TD waste but this was not
logged.
> COP: TD:HB:270 version III, effective 30/06/93 does not refer

Marki Bence
John Kane

- to the temperature at which the autoclave operates.
- > all essential records of the autoclaving process were available, but the process could be greatly improved by designing a record sheet that incorporated eg the autoclave run number; run contents, the spore check/results, and a signature, indicating from the temperature chart that the time and temperature requirements were met (or otherwise).
- 2.46 "Calling the Bank" > It is recommended that consideration is given to developing a system of reconciliation eg what was received at the Centre vs what eg was removed because of TD results, syphilis, blood grouping, held in quarantine, burst, and available for issue.
- > only the last 3 digits are called (other than at the start of the process). Some thought should be given to assuring the security of this operation.
 - > when checking suitability on the L592/93 worksheet, it would seem that a rule should be used to gain a clear view of all results for each donation. Otherwise, in view of the amount of data on the sheet, it must be more difficult to complete the exercise.
 - > the labels, and especially "suitable for transfusion" and "tested" labels were loose and uncontrolled.
 - > formica facing coming off benches. Also, the area on which final release was performed needs more attention - cleaning, freedom from scores/grit etc.
- 2.47 QA Staff seemed to be unclear which code, memo, guideline, was to be used and implemented eg National CRC; Canadian BoB; USFDA; AABB. this was considered unhelpful, even counterproductive to GMP compliance.
- 2.48 QA There was no system in place to ensure that unauthorised copying of controlled documents (SOPs; COPs and the like) could not take place eg use of a coloured stamp or coloured paper.
- 2.49 QA There was no formal review process for COPs. This should take place at least annually and there should be a system to manage the review process.
- 2.50 QA Records of issues of some controlled documents eg National SOP NSG:100 had pencil entries. All entries must be permanent.
- 2.51 QA The listing of staff signatures did not appear to be updated on a regular basis eg the list "printed 27/4/93" had an extra name added to the list dated "6/94".

- 2.52 **QA** Inadequate arrangements had been made to provide the QA Specialist with sufficiently comprehensive GMP training for a blood transfusion centre.
- 2.53 **QA** Some inspections had taken place but there was no formal programme of internal audits.
- 2.54 **QA** Whilst validation is now being introduced, it is clear that the Centre will need to develop and implement a much more formal process that will involve the QA Manager.
- 2.55 **QA** There are no COPs for the recall of fractionated products or of fresh blood products.
- It appears that, at present, these are primarily handled by the "Production" Manager (ie Laboratory Manager) [and handled very effectively]. The arrangements for dealing with such problems out of normal hours are not acceptable, being handled by the commitment and generosity of the Laboratory Manager. An appropriate rota system should be developed and formalised.
- 2.56 **QA (QC)** There is no COP for dealing with sterility test positive samples. (Although available records suggest these are handled very well).
- 2.57 **Training** Whilst there was good evidence that training and training needs are being addressed there was a lack of evidence that this was being controlled by a cohesive, well managed plan.
- This aspect requires further thought and development - that should include a measurement/review feedback loop.
- 2.58 **Product Management** Procedures for managing the inventory of fractionated products were considered secure. However, the daily record of transactions showed regular errors (which were corrected at a later stage), the product/lot record cards had occasional corrections to totals but no explanation given to confirm satisfactory action had been taken. Some record cards had "white-out" corrections. A computerised system was being introduced (in two weeks time).
- 2.59 **General** As a general remark it seemed that much equipment in the Centre was old and in need of replacement eg the BG15; some really old centrifuges (without lid locking devices); the Haemonetics V50; chest deepfreezers.

Most of the storage cabinets could be locked and it is recommended

this is pursued.

2.60 **National -
Uplift of
RP/RP15**

The contract refrigerated vehicle arrived at Saint John to collect plasma for fractionation and an opportunity was taken to view this (Arctic Star Refrigeration Express).

There is a temperature display in the driver's cab and on the compressor unit outside. There was no high temperature alarm in the cab (although loss of power etc activated such an alarm).

It was indicated that plasma loading could not start until the storage area temperature was -4°F (-20°C) or colder. Before opening the tailgate, the driver suggested that "we might find a few boxes on the floor since the road from Halifax is rough and there is no way of tying the boxes in".

In the event there were several boxes of plasma that had fallen from a stack onto the floor. An attempt had been made to support stacks of plasma boxes by placing wooden palettes against them. This is not satisfactory and the scale of the problem should be investigated.

A probe and a clockwork temperature recording device were held in a wooden box in the storage compartment. This had been calibrated April 1994 - there was no indication of next due date. The chart was not dated to indicate when it was started and the trace was hardly visible.

The driver thought that when the trip was complete, his office would fax a copy of the chart to the Red Cross in Ottawa. Boxes of plasma were stored against the sides and back of the storage unit.

*Martin Byce/
Helen Ross*

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT OF SAINT JOHN CENTRE

24 - 28 OCTOBER 1994

APPENDIX 3

INTERNATIONAL CHECKLIST

Martin Byrce
John Rarr

**COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA:
INTERNATIONAL AUDIT TEAM CRITICAL CONTROL POINT CHECKLIST**

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
1. DONOR SELECTION				
1. Is there an effective donor deferral procedure	UK; CDD; USFDA	✓		1.1.1. This includes a procedure for <u>self</u> deferral
2. Is there a register of donors with a history of repeat reactivity in mandatory microbiological screening tests?	USFDA; UK	✓		1.1.2. Kept on microfiche and hard copy, updated fortnightly
2 Do donor assessment areas provide an adequate level of privacy? ie can waiting donors <u>see</u> the completed questionnaire or <u>overhear</u> verbal questions and answers?	CRCS; UK; ATGA; CRCS; WHO; USFDA; CDD	✓		1.2. Privacy behind interviews screens could be improved by placing a radio outside.
3 Are prospective donors provided with information on AIDS/high risk activities at each donation?	USFDA; UK; ATGA; CRCS; EC	✓		2.2. Yes, but occasional unlabelled satellite bags picked up at the checking desk.
4 Do donors acknowledge in writing at each donation that they have read and understood the "health check"/"fit to donate" criteria?	USFDA; UK	✓		2.3.2. Have not validated this procedure.
5 Are donors made aware that recipients experience risk from transfusion and are they, therefore, asked to report any illness developing subsequent to the donation?	UK; ATGA; CRCS; CDD	✓		3.1 Not adequate. National SOP requires donor identification but does not specify the requirements. Local interpretation is "Hello Mr. _____ how are you today?"
2. PREPARATION FOR VENESECTION				
1 Are blood packs inspected before use to ensure they are: 1. in date?	EC ATGA; UK	✓		3.4. Double check by a second, independent person (see also 2.2).
2. free from defects?	ATGA; UK; EC	✓		
2 Is there a secure procedure to ensure that donor records, blood packs and sample tubes are correctly labelled at the time of donation?	UK; USFDA; EC; CRCS	✓		
3 Is the procedure for arm preparation: 1. appropriate?	USFDA; UK; EC; ATGA; WHO; CDD	✓		
2. validated?			✓	
3. BLOOD COLLECTION				
1 Is the identity of the donor checked before venepuncture?	ATGA; EC; UK		✓	
2 If local anaesthetic is used, do the procedures for preparation and injection: 1. follow "clean" procedures (aseptic)?	ATGA, EC	N/A		
2. explicitly exclude resheathing of needles?		N/A		
3. avoid any chance of donor/donor cross infection?	ATGA	N/A		
3 Are the donor attendant duties organised so as to prevent any mix up in documentation, samples or labelling between donors/donations?		✓		
4 Is the donation number checked on all items to ensure that those on the blood packs and sample tubes are identical with those on the paper work?	EC; UK	✓		

COMMENTS - IDENTIFY BY NUMBER

N/A = NOT APPLICABLE.

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Are any excess labels defaced/destroyed immediately after labelling is complete?			✓	3.5. (see also 2.2 & 3.4) Occasionally, labels are retrieved from the waste container and attached to packs from which they had been omitted. Also, multiple unique donation numbers are attached to the primary pack and used throughout various stages of the testing process / manufacturing.
6 Once the donation is complete is there a procedure that requires the container, samples and documentation, especially labels, to be checked for defects?	EC; USFDA	✓		
7 Adverse Donor Events 1. Is there a written procedure for resuscitation?	WHO; CDD		✓	
2. Are staff trained and annually updated in resuscitation techniques?	WHO	✓		
3. Is there a written procedure that requires the components of the resuscitation "kit" to be checked on a regular schedule and logged?		✓ N/A		3.7.2 There was no record of CPR training for physicians.
4. TRANSFUSION MICROBIOLOGY				4.6 Manual addition takes place for confirmatory repeat testing procedure seems secure.
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA	✓		
2 Are tests performed on samples taken at the time of donation?	WHO; USFDA; CDD	✓		
3 Are reagents used as recommended by the manufacturer?	USFDA; UK; CDD	✓		4.7. Samples for lot preacceptance testing came from National or, for anti-HCV, from <u>Oerho</u> . i.e. the test kit manufacturer.
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA	✓		
5 Is there a secure system for keyboard entry of numbers?		✓		
6 Are samples ever manually added to test wells? If yes, describe the circumstances and procedures.		✓		
7 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes: manufacturers? in-house? licensing/national authority? how frequently tested?	UK; ATGA; USFDA; EC	✓ ✓ ✓ ✓	✓ ✓ ✓ ✓	
8 Is a system of positive reporting used? (ie are results recorded for all samples)	UK	✓		
9 1. If results are interpreted by computer software, is this validated?	CRCS; UK	✓		
2. If results are interpreted manually, is this governed by a written procedure?	UK	✓		
10 For initial screening test positives and previously recorded positives, is there a secure procedure for ensuring that the correct samples are retrieved for repeat testing?	UK	✓		
11 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS	✓		
12 Are there secure, written procedures that permit the identification of all subcomponents of a donation and ensure their retrieval, disinfection and disposal?	UK; CRCS; USFDA; WHO	✓		

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
13 For components in long term storage, is there a secure procedure for storage, retrieval, testing and reporting of archive samples?			✓	4.13. Archive samples are not retained.
14 Are test data reviewed by personnel before final results are reported?	USFDA; UK	✓		4.17. Yes, but the editing is done by one person to be checked possibly one month later by computer services.
15 Do repeat reactive results produce a rapid deferral flag in the donor record?	UK	✓		Double check at time of entry has been recommended.
16 If confirmatory testing of positives is performed off site, is there a secure, written procedure for preparing and labelling samples?		✓		4.18. But, as required by National, there is such a procedure for anti-HCV repeat reactives.
17 Is there a secure, written procedure for inputting and editing donor files on receipt of confirmatory test results.		✓		
18 For HBsAg and anti-HIV 1 + 2 repeat reactives, is there a written procedure to ensure that any previously prepared component still held in inventory is quarantined?	USFDA		✓	5.3. Antiserum reagents are diluted/formulated but there is no adequate record of this process. QC is performed but not in the form of an acceptance for use check.
5. BLOOD GROUPING (ABO & RhD)				5.4. The automated blood grouping system (Ba15) is 20 years old and the sequential numbering system is not secure. The system does not provide positive sample I.D. Security is provided by multiple manual checks of numbers.
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA	✓		5.6 Controls prepared in house from donated red cells - not adequately labelled.
2 Are tests performed on samples taken at the time of donation?	USFDA; WHO	✓		6.1. The procedure involves a search of various paper records / worksheets but is satisfactory.
3 Are reagents used as recommended by the manufacturer?	USFDA		✓	
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA		✓	
5 Is there a secure system for keyboard entry of numbers?		N/A		
6 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes, describe: controls used their source how frequently tested	UK; ATGA; USFDA	✓		
7 1 If results are interpreted by computer software, is this validated?	CRCS	N/A		
2 If results are interpreted manually, is this governed by a written procedure?		✓		
8 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS	✓		
9 Are test data reviewed by personnel before final results are reported?	USFDA; UK	✓		
6. COMPONENT PREPARATION				
1 Is there a procedure that ensures a rapid and effective reconciliation of all components at all stages of their manufacture?			✓	

COMMENTS - IDENTIFY BY NUMBER

N/A = NOT APPLICABLE

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
2 If an open processing system is used; 1. is component sterility testing performed?	UK	✓		6.2 Some, but inadequate, precautions taken. System needs to be reviewed.
2. is environmental monitoring performed, especially during the open procedure?	UK		✓	
3 If a sterile connecting device is used 1. is the system validated?	UK	N/A		6.4. Performed very infrequently, procedure not reviewed.
2. what is the validation interval?		N/A		
4 Where component preparation requires relabelling of a pack eg for washed red cells or for pooled platelets 1. is this governed by a written procedure?	UK			7.1. Secure but involves an excessive amount of manual transcription.
2. is the procedure secure?	UK			7.3/7.4. Not raised.
7. COMPONENT LABELLING & RELEASE TO STOCK				8.2 Temperature monitoring arrangements for frozen material, in particular chest deepfreezers, needs to be reviewed.
1 Do procedures ensure that components cannot be released to stock until all the required tests (mandatory and additional) have been completed, and records reviewed, with satisfactory outcomes?	UK; USFDA	✓		
2 Is the procedure for labelling blood components? 1. a written procedure	USFDA	✓		
2. secure?		✓		
3. followed?		✓		8.3. Only annual check but no accurate validation is possible for chest freezers. (Probes are concealed, location is unknown, cannot be accessed).
3 In exceptional instances are components issued when they do not conform to mandatory requirements (eg test results not available). If yes, is this governed by a written, secure procedure?	UK; USFDA			
4 Are blood components ever received from non-Red Cross blood collection facilities? If yes, is this covered by a written, secure procedure?	CRCS			
8. COMPONENT STORAGE				
1 Do blood component storage areas and procedures allow for appropriate segregation and effective identification of components of different status eg 1. untested	UK, CRCS EC; USFDA; CDD	✓		
2. "hold" status		✓		
3. Biohazard		✓		
4. available for issue		✓		
2 Are arrangements for monitoring the temperature of blood component storage areas adequate?	CRCS; UK; CDD		✓	
3 Are monitoring systems and alarms regularly validated to ensure functionality.	EC; UK		✓	

COMMENTS - IDENTIFY BY NUMBER

N/A - Not applicable.

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
9. INFORMATION TECHNOLOGY				
1 Has the computer system been validated to provide assurance that the system operates properly in the intended environment? If yes, is this documented?	USFDA; ATGA USFDA			<p>9.1. Source code for BLIS is held at National. They undertake all validation, change control etc.</p> <p>9.3. Manual from National is a "programmers guide". Development of an in-house manual is progressing.</p> <p>9.4. In their specific use of the system</p> <p>9.5. Requirement to change password regularly has been deleted due to a problem with a computer virus on BLIS.</p> <p>9.6. Only input of Rn group, repeat reactive virology result and donor: donation entering are audit traceable.</p> <p>9.9 No adequately developed disaster recovery plan.</p> <p>10.2 } These systems are 10.3 } presently being developed - if current progress is maintained, should be OK.</p> <p>11.1 } The management 11.2 } arrangements for GMP systems need to be reviewed.</p> <p>11.3 Need to introduce an annual document review process and a mechanism to prevent copying.</p>
Are all changes and modifications that are made to the computer system evaluated to assure that no other areas of the system are adversely affected by the change?	USFDA; CDD			
2 Did the validation reflect normal, stress, exceptional, boundary and invalid conditions?	USFDA			
3 Is the computer system covered by an appropriate users manual?	CRCS; ATGA; EC; USFDA; CDD		✓	
4 Are users of the system given adequate training?	CRCS; USFDA	✓		
5 Does the system have security procedures to prevent unauthorised access?	USFDA; ATGA; CDD; CRCS; EC		✓	
6 Is an audit trail maintained so that all changes made to the data can be traced?	ATGA; USFDA		✓	
7 Is there a procedure for reporting problems with the system?	USFDA; CRCS	✓		
8 Are written change control procedures available and effective?	USFDA; ATGA; EC	SEE 9.1		
9 Are there recovery procedures to return the system to its previously operating state without loss of function, reliability, data or memory?	ATGA; EC		✓	
10 Is barcode quality/readability monitored?				
10. TRAINING				
1 Do employees have appropriate education, training and experience?	USFDA; EC; CRCS; WHO; UK; CDD	✓		
2 Does the training programme include an annual performance review and identification of training needs?	CRCS; CDD		✓	
3 Is employee training documented?	CRCS; UK; CDD		✓	
11. QUALITY ASSURANCE				
1 Is there an individual responsible to management for quality who is independent of production/manufacturing?			✓	
2 Does this individual have sufficient authority to function effectively?	EC, ATGA		✓	
3 Is there a system to control the review, issue, use, retrieval and storage of documents?	UK; CDD	✓		
4 Is there a programme of self inspections (audits).	EC, UK; CDD		✓	

COMMENTS - IDENTIFY BY NUMBER

11.4. Some ad-hoc inspections have taken place internally but an internal inspection programme has not been developed.

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Is there a procedure to ensure that new equipment, tests or procedures are validated 1. before being introduced for routine use?	EC CDD		✓	11.5 Validation has been done but mainly on an informal ad-hoc basis. This needs to be reviewed.
2. After repairs or readjustments which may affect performance.				
3. If any problems are suspected.				
4. Does the procedure include the production of a validation report that indicates authorisation is given to introduce (or not) this new piece of equipment/test/procedure, the date of authorisation and the date of introduction?				
6 1. Is there an effective, written procedure/s for product recall?	UK		✓	11.6.1 The procedures followed internally (from records viewed) are thorough and secure but are not written. 11.6.8 Arrangements are made but are not formal.
2. Do the recall procedure/s apply to fresh blood components and fractionated products.			✓	
3. How often has the procedure been used in the last 12 months for: blood components? fractionated products?		x2		
7 Is there an effective, written procedure for reporting adverse reactions to fractionated products, blood components?	CDD; USFDA		✓	
8 Is adequate provision made to support these adverse reaction/recall procedures out of normal working hours?			✓	
9 Is there a consistent approach to GMP (across all component/product types and processes)?		✓		

COMMENTS - IDENTIFY BY NUMBER

STRICTLY CONFIDENTIAL

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL INSPECTION TEAM: AUDIT OF WINNIPEG
31 OCT - 03 NOV 1994GENERAL SUMMARY

The Management Board at the Winnipeg Centre included two managers who had recently joined the Centre (Laboratory & Nursing), therefore it was not easy to assess how the Board were functioning as a team. There was, however, a clear commitment to performance improvement and evidence that the Centre was making progress towards this goal.

Staff within the Centre have been working very hard to develop an understanding of the concept of GMP and to develop systems that comply with this concept. Whilst there was evidence that progress was being made, the extent to which GMP was being applied varied from a very high level, through developing systems to non-existent.

The number and nature of important GMP non-compliances recorded at audit was a serious cause for concern. However, the absolutely crucial activities of blood collection, laboratory testing and release of components to stock were judged to be governed by secure systems and with this qualification, the auditors concluded that these systems were sufficient to ensure the provision of a safe blood supply from the Winnipeg Centre.

Against this background, the reported GMP non-compliances should be viewed in the context of providing opportunities to build a GMP approach around these secure foundations.

Of the GMP deficiencies identified, an effort has been made to classify them into "Principal Matters of Concern", "Other Major Matters of Concern" and "Other Points of Concern". The purpose of this classification was to help the Winnipeg team focus on dealing with the major issues (the first two categories) whilst providing details of every conceivable improvement opportunity (the latter category). It must be stressed that many deficiencies in this latter category would not normally be documented by the auditors. (Responsibility for doing so would reside with the auditees). In this instance we considered it would be more helpful to list everything.

It was clear to the auditors that multiple inspections, continued adverse media coverage and pressure to implement imposed changes were producing major challenges to systems and staff in the Winnipeg Centre. Consequently, the auditors wish to emphasize that the deficiencies reported by them should be carefully reviewed by Centre teams and any changes that result should follow a carefully planned and structured process, to be completed in a reasonable timeframe.

Seventeen non-compliances were listed as Principal Matters of Concern and a further seven were listed as Other Major Matters of Concern. The number and type of deficiencies

recorded are in keeping with the auditors' concerns that, in general, the Centre is struggling to cope with considerable change, including the development and implementation of systems that comply with GMP. Nevertheless, it is important that the Winnipeg team focus on the auditors' assessment that their critical functions are in control and with that assurance they should move forward in a planned and very positive manner.

Furthermore, the extent to which National feature in these GMP non compliances should not pass without comment, nor should the auditors' conclusion that the current premises are not of an adequate standard for manufacturing blood components in compliance with GMP.

Detailed descriptions of the "Principal and Major Matters of Concern" are given in appendix 1. The "Other Points of Concern" are shown in appendix 2. The completed checklist is attached as appendix 3.

Throughout this process, all staff contacted conducted themselves in a highly professional manner and their patience, co-operation and eagerness to help did much to facilitate the audit process. The auditors would like to express their sincere thanks for the assistance given.

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT OF WINNIPEG CENTRE

31 OCTOBER - 03 NOVEMBER 1994

APPENDIX 1

PRINCIPAL AND OTHER MAJOR MATTERS OF CONCERN

Martin Givens
Arthur Hare

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM: AUDIT OF WINNIPEG
31 OCTOBER - 03 NOVEMBER 1994

1. PRINCIPAL AND OTHER MAJOR MATTERS OF CONCERN

1.1 PRINCIPAL MATTERS OF CONCERN

1.1.1 "Spare" Unique Donation Numbers

A set of unique donation numbers are stuck onto the reverse side of the primary pack at collection. These numbers are used at various points during the manufacturing process (to stick onto packs, sample tubes, worksheets etc), but there is no control over/record of their usage. In GMP terms, reconciliation of labels is fundamental and the ideal would be to destroy any surplus labels at collection.

Justification for the auditors' concern over this matter was noted when red cell components were being sorted for final clearance. A number of instances were observed (7 out of 88 approx) where barcode numbers had become detached from the back of one pack and had stuck onto the front of another eg pack # [4]785121 had label # [6]785122 on it, this was removed. Similarly #... 104 had label # [5]785117; #... 119 had label # [2]785106; #... 191 had label # [1]785115.

One of these labels ([6]785122) was not defaced before being put into the waste bin.

Since these components are handled in storage in a similar manner pre and post labelling for release, this must be a continual problem within the Centre and at hospitals. (At the post audit meeting the Laboratory Manager confirmed this was indeed a problem for hospitals).

1.1.2 Premises

The premises did not meet the standards required for manufacturing in compliance with GMP eg

> in the component processing laboratories

the centrifuge/separation room was very cramped and did not lend itself to cleaning; the floor was unsealed and in one area tiles were curled back from the floor allowing dirt to accumulate. The ceiling tiles were in a very poor condition and there were numerous gaps; benches were chipped and Formica facings had come off exposing bare wood; paint on windows/ledges was flaking. The air conditioning system down-drafted unfiltered air directly onto a processing area; the

windows had blinds which were very dirty.

similar comments apply to the adjacent components laboratory.

- > due to constraints of space, various items such as platelet incubators and refrigerators were stored in corridors.
- > the stores areas were especially bad. Lack of space demanded that goods which required specific storage temperature were held in areas that were too hot or too cold. There was insufficient space to operate an effective stores operation and goods received of necessity "often" sat in the corridor beside the rear door. At inspection this corridor had been virtually blocked for more than 1 day. This was a fire escape route.

1.1.3 Procedures for Freezing/Thawing and/or Washing Red Cells for Transfusion

These procedures involved open processing by procedures that were not acceptable.

Glycerolisation was performed according to COP LT/QC/003 version 01, effective 12 Oct 1993. This procedure was carried out in an open corner of the red cell investigation laboratory underneath an air conditioning vent. The COP does not require gloves to be worn. Red cells and glycerol were required to be brought to 37°C in a small waterbath - there were no validation data to support the time of incubation in this small bath. It was not known if the water contained any bactericide/bacteriostat but the water was said to be changed weekly. There was no bacteriological monitoring of the water or processing environment.

Deglycerolisation of frozen cells and washing of cells for transfusion was performed in the "Stem Cell Room". This had a laminar flow cabinet but this was used for stem cell work only. the deglycerolisation process was governed by COP LT/QC/004 version 01, effective 17 July 1993. This carried numerous unauthorised pencil comments. The procedure did not require the frozen red cells to be placed into an outer bag before placing in the waterbath to thaw. There was no bacteriostat/bactericide added to the water and no monitoring of the water or processing environment for bacterial contamination.

The washed red cell procedure was not reviewed but it is understood that many of the points raised above will apply.

Whilst sterility checks do not indicate any problems, it is recommended that these processes are reviewed and changes implemented in a controlled manner to bring them into GMP compliance.

1.1.4 Lack of Expiry Dates

Fresh blood components do not carry an expiry date. This is contrary to GMP and

conflicts with Canadian Red Cross Policy ie Circular of Information for the use of Human Blood and Blood and Blood Components, February 1994, page 4, A.3.7. (Blood Component Labelling, "Labels contain the following information #7 The expiration date).

This point is important for, as is pointed out in the CRC Clinical Guide to Transfusion (3rd Edition page 5, 1993), storage time will vary with the suspending medium and pack formulation.

1.1.5 Storage of Albumin, Pentaspan etc

Arrangements for storing non-refrigerated therapeutic products were not acceptable (eg albumin, Pentaspan). Boxes of such products were stored directly on the floor in an area that also contained supplies for the Manitoba Red Cross.

Management have not ensured there is an effective temperature monitoring system in this area. The area had a max/min thermometer and no alarm. It appeared to the auditors that the storekeeper had received no instructions on how to read this thermometer properly and the recorded temperature (on a handwritten sheet, not part of a COP) was a single temperature.

Maximum and minimum temperatures were not being recorded and the max/min indicators were not being reset at each reading. The thermometer did not carry a calibration tag to show it had been calibrated to the reference temperature standard. At audit on 02 November 1994 the thermometer showed a maximum of approx 26°C and a minimum of approx 8°C.

Pentaspan lot #D3 LO87152, expiry Jun 1995 was stored in this area. It had a recommended storage temperature of 15°C - 25°C.

1.1.6 Blood Component Storage

> Alarm System

The alarm system (Rees, computerised alarm) could not be shown to be checked regularly since it had only been installed in April 94 and checks were to be done at 6 monthly intervals (now overdue). This was considered to be too long an interval at present - more frequent checks should be introduced until the operation of the system is fully established.

It was considered that too many staff (14) had (hierarchical) access to de-activation of the alarm system. This should be restricted to a few key personnel.

It could not be demonstrated that the computerised alarm system was understood fully by the staff who operated it. There was no COP for

*Martin Bruce
Belin Rose*

operation the system and the emergency plan for out of hours problems (COP/607; 26/9/94) had not been seen by the 2 staff responsible for the alarm system (Central Administrator & Building Manager) until the audit.

> **General, Storage**

Each area checked their own temperatures and charts - there was no one person with an overview or in overall control of the system

eg with respect to emergency power.

- . records did not easily show which equipment was on the emergency power circuit.
- . after trying unsuccessfully to locate a particular piece of equipment it was found to have been relocated without changing the appropriate documentation.
- . due to different numbering systems, the current list for the alarm system could not easily be cross referenced to the list of emergency power equipment.
- . some equipment on the "alarm" list was not correctly described eg #27 was noted as "Quarantine platelet cabinet" but was later found to be "released".
- . storage units were not adequately labelled to describe their contents.
- . there was no emergency power supply to fridge #22 (cryo thawing), to the 3 platelet agitators or to the red cells frozen at -65°C in freezer #46.
- . no temperature mapping had been done and as a result there were no load limits on chest freezers. Plasma was stored against walls and floors of freezers and up to the freezer lid (eg #20, 25).
- . in general, refrigerated storage containers were not cleaned, required defrosting, had ice on the floor (walk-ins). Boxes and plastic bins containing components were stored directly on the floor.
- . there was no adequate system for reporting actions taken in response to requests for maintenance assistance eg #5 had been reported seven times to maintenance due to problems with recorded temperatures. Staff who reported these problems received no information concerning (corrective) action taken by maintenance.
- . there were no procedures to detail what maintenance was carried out at 3 monthly intervals.
- . due to lack of space there were no back-up compressors for any of the walk-in cold rooms/freezer.

*Martin Gurr
Alan Rann*

1.1.7 Storage - General Supplies

Supplies were held in 3 separate rooms, none of which were suitable for that purpose.

1. The area which housed the compressors for walk in fridges/freezer and Instacools was also used as a store room. The room was hot and dirty - there was no temperature monitoring of any kind.

Supplies in this room included Javex which the manufacturer had labelled "STORE IN A COOL DARK PLACE"; and cotton wool balls which were used by blood collection staff. The compressors etc in this room had no protective coverings.

2. Warehouse 1 contained, amongst other material, blood packs, apheresis harnesses, anticoagulants and saline. Heating and hot water pipes run across the ceiling and there were others on the walls. The room was hot but there was no temperature monitoring.

There were:

- . two large convection heaters, one of which was switched on and venting hot air onto stored product - Immuno saline, lot #94 01134, which had a recommended storage temperature of 10°C - 20°C. This limit clearly was being exceeded.
- . an open exhaust fan extractor.
- . a vacuum pump for the crossmatch lab which was exhausting apparently unfiltered air into the room.
- . a floor drain with a vented grating which was said to connect to the sewer. A "flashback" situation could not be denied as a scenario during floods.
- . there were holes in the ceiling, walls and floors and a large number of cartons were stored directly on the floor making thorough cleaning impossible. The area was dirty.
- . there were unprotected light bulbs and missing bulbs.
- . the area contained a large quantity of combustible material but there was no fire extinguisher.

There was a very large stock of blood packs and apheresis harnesses causing them to be stacked almost to the ceiling, sometimes against or very close to hot pipes. There was no temperature monitoring but it was considered that particularly near the ceiling (where the pipes were) the storage temperature was too high.

The large stocks of such materials were causing serious storage

*Martin Bruce
Kevin Rane*

problems/congestion but National had directed that Centres must carry a 3 month stock - an appropriate regular delivery arrangement with the supplier would be preferable.

This congestion was further compounded by a stock of harnesses for Baxter apheresis machines which were no longer needed (due to the National switch to Haemonetics) and which National had advised would be collected by Baxter.

There was no quarantine storage area and no procedure for marking material that was "non conforming" eg

At the end of the room was a stock of boxes of single packs. This stack contained -

- . 4 cartons of lot #CA1J29 that expired 8/94
- . 1 carton of lot #CA1M64 that expired 10/94
- . 2 cartons of in-date packs

There were 3 foil pouches containing single packs on top of another stack of boxes - these foil pouches expired 8/94 (all lot #CA1J29).

One foil pouch of apheresis packs had been sent down from the donor clinic to be returned to Baxter but was not marked to indicate it should not be used.

An inventory record dated 03/02/94 did not list an item being stored in Section PH21 of this room. This was an open box full of connection tubes (lot #72050, N2 B1J 0250 Pharmareal) that nursing staff advised were used in therapeutic apheresis but they had stopped using them over 3 years ago.

3. Goods Inward

There was no formal procedure or adequate space for handling incoming goods. Material was unloaded directly from the back door into the "receiving" corridor. This door had several gaps and cold air was drafting in. At inspection a consignment of apheresis harnesses and Nutricel packs from Miles had been delivered. Both consignments were stacked directly onto the floor and were about 7-8 feet high. The stacks were insecure. This corridor had been almost full with these goods for over a day and appeared to be a fire escape route. The area was cold (because of the unsealed door) except for heat being convected onto some boxes by a power filter for computer services. It was considered that creating sufficient room in warehouse 1 to house these goods would be a major undertaking that would require a considerable amount of work. It was not known how long consignments of goods would be stored in such uncontrolled conditions or how frequently such situations arose.

*Martin Bruce
Allen Rave*

There were no COPs to indicate how this area should be ordered and managed, particularly to ensure stock control and rotation in compliance with recommended storage requirements.

1.1.8 National SOPs and Directives

There was much evidence that the issue of SOPs and Directives from National was causing problems in Winnipeg eg

- > changes to document numbering system caused problems with indexing and control
- > there were unreasonable demands to implement changes rapidly eg with respect to the "double scrub" arm preparation procedure, covered in SOP NSG:180, the implementation date was 01 Nov 1994. Staff in Winnipeg had implemented a local procedure (NM 800: version 1; effective 01 Nov 1994) to cover this change but the process had not been validated, training had been given but there was no time to document this prior to inspection and the procedure was in use on 31/10/94 (effective date for NM800 was 01 Nov 1994).
- > some of the validation tests being performed in the TD lab were causing problems eg with respect to the volumetric calibration of the Cavro with Methyl Orange, National issue a range of OD that must be met which is not realistic. It is understood there may be variability between diluters and in-batch variability of the methyl orange eg age, how stored and handled. It was noted that the equipment manufacturer considers the volumetric system is unsatisfactory.
- > new barcode labels for plasma for fractionation were introduced within the last week or so. These labels carry two eye readable numbers and a barcode. eg

540 O 9 785096



40 55 785096-2

These numbers clearly are different and it is understood that the barcode decodes as the bottom number. Issuing different numbers on the same label and label set is potentially dangerous and this has been compounded by a complete lack of information and guidance by National. (It was understood that some verbal information was given at a National Nurses training session in Ottawa 31 Aug 1994). The auditors established these new labels were received in the Centre's store on 28 Sept 1994).

On discovering this change, the Assistant Laboratory Manager phoned National to establish the reason for this change and as a result, issued a memo on 27 October 1994 to the Components Laboratory Staff. This was not copied to the QA Manager, Laboratory Manager or any other party. There was no opportunity to implement a change control process for COPs or to identify

*Markin Bruce
Helen Rana*

needs for/undertake any training that might have been required.

1.1.9 General Management/GMP

Although the position of QA Specialist is fairly new and continues to evolve, this individual has insufficient authority/responsibility to function as a QA Manager within a system of GMP eg processes were being implemented and communications sent without contacting/discussion with the QA Specialist.

Also, it was considered that an objective review of all lines of reporting and responsibilities could be helpful eg was it appropriate for the Centre Administrator to be responsible for the Temperature Alarm System?

It appeared to the auditors that although some areas of excellence were observed, the Centre was struggling to comprehend the principles of GMP and to design, implement and maintain systems that were in compliance with those principles eg various instances were noted where staff were trying to inspect out problems rather than identifying and eradicate the cause.

1.1.10 Documents & Control

There was no adequate control of documentation eg numerous SOPs in the blood collection area had been copied, deleting important information from the bottom of the page. There was no system to prevent copying and no regular review process. Many procedures in the TD lab were in the form of uncontrolled Training Manuals rather than COPs.

1.1.11 Product/Component Recalls

The "recall" of factor IX, Immuno; lot #050991035 was reviewed. The file contained an issue/returns summary sheet. This had no product identity, lot number and was not signed or dated. The complete procedure was not pursued under the direction of the QA Specialist nor were the completed records reviewed.

At inspection a discrepancy was noted between the figures on the issue voucher and those on the summary sheet for 30 April 1992. The voucher showed 32 units had been issued, the summary sheet stated 31. This discrepancy was not noted therefore 1 unit of product is unaccounted for.

The information on file suggests that there is no good system for recording re-issue of returned product although the policy of re-issuing returned product should be placed under review. There was no COP for handling recalls of fractionated product or of fresh blood components (other than for those that result from donor telephone calls post donation).

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1.1.12 Checking Donor Registration Forms

It was noted that a final check (visual) that the donor registration form had been satisfactorily completed was done in the admin (computer) area and that a record was kept of any errors noted. The clerk stated that occasionally a nurse would come in to sign any record entry that was missed. This would take place after the donor session. It was noted that since June 1994, ninety three errors had been recorded (eg [3]330243). As this was the third check of this documentation the need for staff training in the use and checking of this form must be an important issue.

There was no COP to detail what action was to be taken by the clerk if an error was noted.

1.1.13 Health and Safety

A number of health and safety matters were raised these included

- > staff in the blood collection dept do not always use needle guards. There is no mandatory requirement to do so. A number of needlestick injuries were said to be recorded each year.
- > a consignment of blood packs were stacked in an insecure manner to about 7-8 feet in a corridor that appeared to be a fire escape.
- > the building had no fire alarm system and did not seem to have adequate fire fighting equipment.
- > machinery in the "cleaning equip" store was unprotected.
- > there was a lack of sinks for handwash only and a "perceived" lack of handwashing.

1.1.14 Therapeutic Plasma

The freezer containing "therapeutic plasma" was considered an unacceptable hazard. There was no inventory of its contents, some of which dated to 1984. The packs appeared frozen together. The freezer was not locked, was not controlled for temperature and no-one knew what it contained. It is recommended the contents are documented and discarded as a matter of urgency.

1.1.15 Transcription Processes

Whilst the transcription processes viewed at Winnipeg were considered to be secure, there is concern at the amount of manual transcription, particularly of machine interpreted results.

1.1.16 BLIS

There were several points of concern relating to the BLIS system eg

- > there was no users manual that covered all areas of application.
- > all information is keyboard entered - although this is double entered, changes due to errors are not logged.
- > duplicate donor records can be produced.
- > password control has not been enforced by National but no-one (in admin) had contacted or had been contacted National to find out why.
- > the complete donation number is not printed on the L 592/93 worksheet.
- > the disaster recovery plan has never been tested.
- > training is given on the live system.

1.1.17 Unique Donation Number

The donor database requires the blood group as part of the unique donation number, therefore new donors/donors without cards must be grouped on session before a number can be allocated.

ABO blood group labels are attached at the time of collection ie before laboratory testing.

A number of grouping errors occur on clinics. The procedures required to correct these errors were complex and time consuming.

1.2 **OTHER MAJOR MATTERS OF CONCERN**

1.2.1 Problem with anti-HTLV I Kits

Problems were encountered with the Organon Tecknika anti-HTLV 1 kits. Lot #121011, received on 12 April 1994 was introduced into routine use on 26 April 1994 and intermittently produced low readings with the positive kit control. This problem was reported to the Manufacturer and National (although this action was not documented).

The TD Charge Technologist was aware that other Centres had experienced the same problem and that they also had contacted National. The short term response to the problem was to continue to repeat each plate of tests until an acceptable result was obtained with the manufacturer's positive control. This continued until a new lot of kits (#121023) was received from the manufacturer on 31 May 1994.

The new lot number continued to provide problems with the positive control and a new consignment of the same lot was received from the manufacturer on 07 June 1994 but was recalled by the manufacturer on 22 June 1994. However, there was no alternative test kit available so lot #121023 (ie the recalled lot no) was used until a replacement (lot #139557) was received on 28 June 1994.

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Alan Rane

It is considered that the time taken to resolve this problem was excessive and is unsatisfactory that throughout the entire process, no advice, comment or information was received from National. It was not known what investigations were performed by National.

1.2.2 Privacy and Procedures for Donor Interview

The rooms in which donor interviews were conducted were "half glass" on three walls and abutted onto one another. It was felt that this did not offer adequate visual privacy. Computer screens could be seen by the donors at interview.

On two occasions during the inspection, young children were seen in the interview room. This practice should be discontinued, especially if the child can in any way understand the questions - this may result in a failure to answer honestly.

1.2.3 Positive Identification of Donors at Collection

Procedures for identifying donors on clinics were not acceptable eg "Hello Mr, how are you today". Donors should be asked to give their name and, at least, date of birth.

1.2.4 Lack of Validation of Component Process

The Instacool freezing process is based on manufacturer's instructions and has never been validated. Only one freezing chamber is fitted with sealed membrane sleeves. In this latter chamber the coolant is raised to completely surround the packs, in the open chamber the coolant does not reach the same level therefore the freezing requirements (time etc) will be different.

The in-house maintenance team serviced these instruments. The service records were observed. Some were roughly drawn on paper and were not part of a controlled document system. An instruction from the manufacturer indicated that with effect from 15 Sept 1993, coolant filtering should be done 6 monthly (previously monthly). Coolant was filtered 14 September 1993 and again on 11 June 1994 (9 months).

There was no record of any maintenance for July or September 1994.

An entry for July 1993 indicated that coolant had not been added because none was available.

There was no validation of the thawing/refreezing process for cryo. Manufacturing records in this area were fairly basic and would benefit from more detail.

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1.2.5 Lack of Validation of Instacool 2 before use

Instacool 2 had been received from Vancouver Centre during the last week of September 1994. The equipment did not appear to have a serial number nor were maintenance records supplied or requested. On receipt it was clear that the equipment was not in working order - the front panel had been removed, neither of the timers worked (parts on order) and one of the pumps was not working (#4, part on order). The compressor unit was relocated to the basement. Despite these problems the unit was introduced into routine use without validation.

1.2.6 Manual Apheresis Materials for Dr Bowman

The area which housed the compressors for walk-in fridges, walk-in freezers and Instacools also was used as a store room. The area was very hot and dirty and there was no temperature monitoring of any kind. On a trolley, stored under a sheet were various items said to be used by Dr Bowman. These included saline (lot #AP420P3 exp Aug 95 - store at 5 - 30°C) and manual plasmapheresis packs (Baxter lot #M92I 14085, exp Sept 95 - store at room temp). Also on the trolleys were pillows. The cover on which the packs of saline & apheresis packs were placed was dirty.

Although it was pointed out to the auditors that these supplies had nothing to do with Winnipeg Red Cross, they were within the Centre and must be subject to consistent rules of GMP compliance that apply within the Centre.

1.2.7 ABO and RhD Grouping of New Donors

Whilst not a requirement in Canada, there was concern that the ABO and RhD groups (D pos) of new donors were tested only once by the laboratory.

*Markin Buice
Helen Rana*

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT OF WINNIPEG CENTRE

31 OCTOBER - 03 NOVEMBER 1994

APPENDIX 2

OTHER MATTERS OF CONCERN

Martin Joyce
Helmut Rave

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA

INTERNATIONAL INSPECTION TEAM: AUDIT OF WINNIPEG
31 OCTOBER - 03 NOVEMBER 1994

2. OTHER MATTERS OF CONCERN

<u>REF</u>	<u>AREA</u>	<u>DESCRIPTION OF PROBLEM</u>
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2.1	Blood Collection	Volunteers at the donor registration desk did not have their own computer account number (log-on code). The computer was set up for volunteers by a staff member. Consequently, audit of data input at this stage was not possible.
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2.2	Blood Collection	Volunteers did not appear to receive adequate training in the donor registration procedure eg they were required to "read and sign" the documents in "Changes to Registration Documentation Procedures". No formal assessment of comprehension was being made.
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2.3	Blood Collection	In the binder which contained "Changes to Registration Documentation Procedures", the page that preceded each document had a list of volunteer names (40). This list was not a controlled document and 5 names had been added after the list was created. It was not known how many of these 40 volunteers were "active". Two documents were reviewed ie
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1. Procedure for Health Assessment Registration of Donors. Ref #NSG/110, effective 22 July 1992 var to version 2.

With respect to volunteers signing to confirm they had read these texts, the earliest signature was 19/09__ (no year), the latest was 19 Oct __ (no year). Neither of the volunteers on duty at the time of audit had signed, indeed 31 of the 40 volunteers on the list had not signed.

Various pages of this SOP (NSG110) had important information missing from the bottom (caused by photocopying) eg effective date, version number, page numbers.

*Martin Bruce
Helen Rose*

2. Procedure for Donor Identification, NSG105; effective 15 May 1992.

Neither of the staff on duty at audit had signed to indicate they had read this document. One signed "on the spot" without reading the text. 25 out of 40 volunteers had not signed.

Clearly, a careful review of procedures is required.

- 2.4 **Blood Collection** Volunteer staff append deferral codes onto the donor registration form. The accuracy of this is not checked until the computer staff enter details on BLIS ie if deferral code was not input on the form or if the wrong code was appended, this would not be noted until much later in the process. These details are available to the nurses performing donor interviews and it would appear more appropriate for them to append deferral code details or, at least, to check the entries made by volunteers.
- 2.5 **Blood Collection** The donor interviewers' initials, not signature, was on the donor medical declaration form. (SOP NSG:110, 22 June 1992 required the signature).
- 2.6 **Blood Collection** No record was made of cleaning in the blood collection area. At audit on 31 October 1994 a spot of blood was noted on one of the apheresis couches which were said not to have been used for several days. There was dirt on the floor behind/under the COBE Spectra machines and it appeared this was not regularly cleaned.
- 2.7 **Blood Collection** Hb (and blood grouping) finger prick samples were taken over the donor paperwork. It was noted that CuSO₄ and 1% Javex were labelled "biohazard". In the UK at least, these are not considered biohazardous. Javex, for example, would be labelled as corrosive.
- 2.8 **Blood Collection** Prior to donation, donors were handed various loose records eg registration form, donation numbers, self exclusion form etc. It was considered that if this practice were to continue, it would be much safer to place all such items in a sealable plastic wallet.
- 2.9 **Blood Collection** The "QC Haemostatic" records lacked clarity eg on 23 Sept 1994 the result was said to be "6.8" but was recorded as "68".

Marki Bence
Helena Kane

The range from the lab was said to be ± 0.6 of the control value but the machine did not read to decimal places and as a result the acceptance range was not clear.

2.10 Blood Collection

A local procedure for the "double scrub" arm cleaning technique had been prepared (Nursing Method (NM) 800:Version 1 Venepuncture, effective 01 Nov 1994 but was in use at audit on 31 Oct 1994.

Staff training in the new procedure had been given but had not been fully documented before implementation. The QA Specialist had not been involved adequately in this procedural change.

The procedure had been implemented to comply with NSG:180 which National directed should be implemented by 01 Nov 1994.

2.11 Blood Collection

No record was made of the venepuncture start time or the duration of bleed. There was no policy for defining a slow bleed although donations were marked as unsuitable for platelets if the bleed was slow. This was not described in a NM (COP).

2.12 Blood Collection

It was said that donors were subjected to only one venepuncture. If unsuccessful the donor was said to be given the opportunity to be deferred off the bed or to volunteer the other arm. It was noted on 31 Oct 1994 that a donor was subjected to a second venepuncture in the same arm.

2.13 Blood Collection

There was a checking procedure at the finishing table however, there was no "NM" to describe the process. There were several important areas where a clear response was not made, with information given by the person doing the work being corrected/clarified by more senior staff present at the audit. These points were as follows:

1. The nursing assistant advised that errors and omissions on the registration forms were taken back to registration for correction. Senior staff disagreed with this response.
2. There was concern that packs with missing numbers may be dealt with by finding and applying the appropriate number and attaching it.
3. With respect to leaks in the bleed line caused by heat

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Adrian Hann

sealing the segments, the local NM which covers this process indicated that the donation should be considered contaminated if the burst is on the pack side of the seal. This needs to be clarified.

All of these points require to be considered, clarified and dealt with accordingly. (See also Principal Matters of Concern 1.1 appendix 1).

- | | | |
|------|-------------------------|---|
| 2.14 | Blood Collection | The "585g calibrated weight" for checking the Sebra collection scales could not be demonstrated to be accurate. This check weight consistently weighed 592g on a balance which could not be traced to a reference standard. The acceptance range was not known and the weight was dirty and was said to have "been used for a long time". There was no NM to describe this process. |
| 2.15 | Blood Collection | National SOP NSG:230, Blood Unit Preparation: copying has removed the SOP number from the bottom of some pages. |
| 2.16 | Blood Collection | There was no written procedure for inspection of blood packs before venepuncture (ie for defects and to check they are in date). This was said to be done at the bedside but was not noted to be done during the audit on 31 October 1994. |
| 2.17 | Blood Collection | The lot number of arm preparation swabs was not being recorded. |
| 2.18 | Blood Collection | There was no validation of the double scrub procedure for preparing the venepuncture site. |
| 2.19 | Blood Collection | <ul style="list-style-type: none">> Biohazardous waste was often not in an appropriately labelled bin eg one bin beside a donor couch contained discarded gloves but was not labelled.> a large bin that was full of biohazard material was left open.> a sharps bin was left open in a corridor near the checking desk where it could easily be knocked over. |
| 2.20 | Blood Collection | There was no records to demonstrate temperature (control) in the collection area. This is important since the area contains working stocks of packs, IV saline and anticoagulants - these have defined storage temperature requirements. |
| 2.21 | Blood Collection | Apheresis donor records were not considered satisfactory eg |

scrutiny of the records for donor #W011422219 showed

1. On 08.11.93 a volume was changed and not authorised by signature. "IgA sent" was said to indicate samples had been sent for immunoglobulins. Although the entry was for 08.11.93, it was not noted until 16 Sept 1994 that these specimens had not been received for testing. Furthermore, the laboratory testing results were indicated by the symbol "-" not "✓" as was used for other entries.
2. Whilst this record form was a National form, the column headings do not reflect the current practices eg "Laboratory tests" are listed as HBsAg; VDRL; HIV although additional mandatory tests are now required.
3. On 31.10.94 under "laboratory tests", there was no tick for HIV, 2 ticks for VDRL and one for HBsAg. The interpretation of these ticks is not clear since they appear to be input before test results are known.
4. There were blood stains on the record and no procedure describing how this should be dealt with.

- | | | |
|------|-------------------------|--|
| 2.22 | Blood Collection | There were unauthorised instructional notes on both COBE Spectra machines. The notes on #1 had one point of information less than did #2. |
| 2.23 | Blood Collection | Nursing staff CPR/First Aid training had not been updated to the required schedule. There was no record of CPR training for physicians. |
| 2.24 | Components | The plasma expressors were cleaned weekly with 1% Javex. This is a corrosive agent and some backplates of the expressors had early signs of pitting and corrosion. It is recommended that backplates are inspected to ensure there are no edges that might cause pinhole leaks to packs. This check should be formally logged. An alternative cleaning agent should be introduced (eg Virkon). |
| 2.25 | Components | There were a number of unauthorised, instructional notes eg on the wall behind the Instacool freezers; centrifugation profiles were taped to the top of each instrument. |
| 2.26 | Components | Room temperature record sheets for the Components Labs were reviewed for October 1994. The specified temperature was 22°C ± 2°C. The following were noted: |

Martin Bruce
Adrian Barr

Room #1 (centrifuges)	Room #2 (freezers etc)
04.10.94 1600hrs 25°C	03.10.94 0800hrs 18.5°C
18.10.94 no entry	04.10.94 0800hrs 19°C
	14.10.94 1600hrs no entry
	28.10.94 1600hrs no entry

On 31 October 1994, both 16.00 entries had been made by 15.50 (the time of audit) - it would be more appropriate to state a timescale during which temperature is recorded rather than a specific time.

It was stated that action had not yet been taken because the sheets were reviewed at the month end by the technologist in charge of the area. However, daily review is essential if corrective action needs to be taken.

In room #1 the thermometer being used was on the wall beside the extract vent for the air conditioning system, therefore the temperature did not adequately reflect the room temperature which was said to be very warm during centrifugation.

2.27 Components

An unlabelled container in the centrifuge room was said to contain all purpose cleaner. A red container said to contain 1% Javex carried only a date (31/10/94). It was not shown whether this was the date of preparation or expiry date.

2.28 Components

Records of plasma freezing were examined for Instacool 1, chamber #2. The COP and manufacturer's instructions recommended 30 mins. However, the following were extracted from the records:

	Time into freezer	Time out of freezer	(Freezing time)
12 Oct 94	0126hrs	0151hrs	<u>25</u> mins
(date not logged by auditors)	0322hrs	0350hrs	<u>28</u> mins

The coolant in Instacool chamber contained a barcode label (#540 O[5]329793) which subsequently was shown to have been there since the plasma was frozen on 13.10.94. This inferred that regular checks of coolant volume and cleanliness were not routine.

2.29 Components

The plasma clearance process was viewed on 31 Oct 1994. 6 boxes of RP.15 plasma were removed from the coldroom and held at room temperature (about 20°C) throughout the checking

process. This involved rechecking RP.15 from quarantine boxes and then repacking. The process viewed (ie for 6 boxes) took about 40 minutes and there was no validation of temperature (ie within the packs) during that time.

This entire process needs to be reviewed eg is it really GMP to stick donation numbers onto the plasma pack before freezing so that they can be peeled off packs after freezing and stuck onto the worksheet? (see also Appendix 1, 1.1.1).

- | | | |
|------|------------|---|
| 2.30 | Components | Plastic bins were used to hold various blood components. These were dirty and were not regularly cleaned. |
| 2.31 | Components | The floor in the "checked" walk-in freezer had about 1 inch of ice and staff were wearing light "day" shoes & trainers when in the freezer. To avoid slipping there was a carpet on the floor directly outside the walk-in freezer. |
| 2.32 | TD Lab | The weekly procedure for the Hamilton AT robotic sampler takes a 10 μ L sample of dye into a 200 μ L volume of diluent. For anti-HIV tests, the sampler takes 10 μ L of serum into 100 μ L of diluent and then samples 10 μ L of this 1/10 dilution into 100 μ L of diluent to make a 1 in 100 dilution. A one off 1/200 dilution of dye does not mimic this double dilution situation. |
| 2.33 | TD Lab | National SOP TD 2000 version 2, effective 22 Feb 93 does not indicate what should be done if the QC of dispense volume verification fails. The (manufacturer's) training manual indicates that the exercise should be repeated no more than twice. If the verification still fails, the tip clamp was to be washed and the exercise repeated. If the problem continued the manufacturer would be called. There was no COP to cover this problem.

Verification exercise records were viewed for both Hamilton AT instruments (#2117 and #2255) both showed several records in which "reviewer sign and date" was not completed. |
| 2.34 | TD Lab | Hamilton AT Service Engineer made a call (#1603) on 26 Oct 94 to investigate a problem with the Barcode Scanner that was failing to read properly the HIV control (well A1) and some of row H. The documented work done by the engineer was "adjusted scanner (scanner no 2119, on AT#2117), for row H, lowered flag control A1, ran PC". |

In such instances, the Service Engineer should be required to provide details of action taken, including validation and should confirm, in the report, that the equipment has been validated post service and is considered satisfactory for use.

2.35 TD Lab

With respect to the ELISA washers, these were said to be checked for pressure/wash volume but this was not logged and the procedure was not part of a COP.

2.36 TD Lab

National SOP, TD5000 anti-HCV, version 4, 19 April 1993 describes (amongst other things) the volume verification procedure for the Cavro diluter dispenser. This requires that 20 μ L of methyl orange is diluted in 217 μ L of water.

The range for acceptable OD is very tight, varies with each batch of methyl orange (and with how old/how stored) and makes no adequate allowance for inter-instrument variation (or from any differences in water/micro plates). Furthermore, the target OD reading for the diluted Methyl Orange was typically 1.3 to 1.4, the typical anti-HCV cut-off was approx 0.6. The manufacturer of the Cavro diluter was said to disagree with this colorimetric verification procedure.

The range of acceptable methyl orange OD was noted to vary with the batch. The current range was 1.379-1.499 and this range was written on red tape attached to the Cavro, there was no methyl orange lot number. Similarly, on the OD printout records, the range of acceptable OD was recorded but the lot number often was not.

2.37 TD Lab

There was no COP to describe the weekly volume calibration checks on manual pipettes of cleaning, said to be done prior to monthly calibration.

Pipette #E130108 (Gilson), single delivery, failed to meet the acceptance criteria at 30 μ L on 14 April 1994 and 12 July 1994 yet staff in the lab seemed unaware of these failures and the subsequent action that should have taken place.

2.38 TD Lab

There was a lack of maintenance records to alert staff how to deal with a fault with the Hamilton AT #2117 ie at audit on 01 Nov 1994, a wash solution error light was "on" due to a faulty sensor. It was said that Sanofi (who service the instrument) had dealt with this problem over the phone some 18 months previously and at that time had advised that saline should be

added to the wash receptacle to "trick" the machine to continue until servicing could be done. There was no written information detailing this advice nor was any record made of when the problem recurred.

2.39 TD Lab

There was concern that the weekly verification of the plate readers for precision, linearity, drift etc, takes readings only from a few wells at 3 wavelengths (450nm, 490nm, 630nm).

This procedure was outlined in National SOP TD2000, version 2, 22 Feb 1993. This SOP contained no indication of action to be taken in the event of a reader verification failure, not was the procedure part of a COP (it was described in the Training Manual).

2.40 TD Lab

Initial Screen TD test positive samples were not entered on the L592/93 worksheet ie a blank box represents a positive test and a comment re the "hold" status is appended to the extreme right of the page. However, for other tests, eg CMV, a blank box on this sheet was said to indicate that the test had not been performed. Test results should be recorded on the worksheet and GMP requires that boxes should not be left blank.

2.41 TD Lab

National provides labels for patient samples that apparently have the same basic barcode structure as donation numbers ie 6 digits plus a check eg 021391-6. Whilst these are visually different from donation numbers, it should be confirmed that these patient label barcodes comply with appropriate guidelines eg ISBT Barcode Working Party; CCBG guide (US).

2.42 TD Lab

The procedure for preparing TD screen positive samples for sending to National involved one operator transcribing the donation number onto a tube with marker pen. Although the documentation was checked before sending to National, this check was not made at the time of labelling and sampling.

2.43 TD Lab

Large distilled water cylinders were not secured to prevent them falling over and causing injury.

2.44 Blood Grouping

Minor improvements could be made to the "reagent production" records in this area ie

- > the batch of saline used to dilute antisera cannot be traced with certainty.
- > there were no recorded details of the filling process/QC

of A₁ and B cells for reverse grouping (2 weeks supply was prepared at a time)

- > red cell controls should have dates put on tubes (perhaps improved labelling could help)
- > the information on reagent preparation pinned to the "notice board" was a permanent record but was not controlled, authorised or dated ie should be part of a COP.

2.45 **Blood Grouping**

There was no local or national policy to prevent the release of plasma that contained potent blood group antibodies (eg anti-D) for fractionation. The Winnipeg Centre occasionally opt not to send plasma containing potent anti-D for fractionation. (anti-D containing plasma is not sent to the Rh institute in Winnipeg who source their own anti-D plasma/donors to make anti-D for prophylaxis).

2.46 **Final Clearance
(Red Cells)**

This process was viewed on 01 Nov 1994 and the following points made:

- > some packs were labelled without removing them from unlabelled packs in the box.
- > the benching was chipped, bare wood was exposed and the floor was dirty.
- > the saline eyewash container on the wall was empty.
- > CMV neg and RhD neg red cells were piled in separate rows to the left of the box containing unlabelled packs. It would be better is these were placed into specific boxes.
- > one operator was noted to sign the bottom of the L592/93 sheet before the column was complete (ie it was done when time was available). The entire process, although clearly a secure routine, was very rapid.
- > plain white labels were stuck onto the pack plastic for red cells containing blood group antibodies of potency < 1/8. The antibody specificity was written on these labels with a biro eg anti-P₁ and anti-C^w. The ink was not indelible.

2.47 **Frozen/Thawed/
Washed RBCs**

Glycerol and saline used in these processes were to be stored at 25°C or below but there was no temperature monitoring in the storage area.

2.48 **QC**

The "Plateletpheresis Record" worksheet was not entirely

Martin Bruce
Helena Harris

satisfactory as a record eg the following were noted on the worksheet for Aug '94:

- > the symbol "-" on the worksheet for WBC count was said to mean a reading "below" 0.000.
- > the donation number, donor's name and recipient's name were entered. This information could not be shown to be necessary in this area and should be excluded from the record to maintain confidentiality.
- > the statement "? sampling error" was not expanded and it could not be demonstrated what this meant or what action had been taken.

2.49 QC

Sterility testing of blood components was performed as per COP QAU/001, version 3, 26 Aug 1994. It was noted that:

- > sterility testing of red cells before freezing involved testing samples taken from segments attached to the original pack, not of the glycerolised cell mixture.
- > the procedure for sampling washed red cells did not specify that the sample should be taken from the cells after washing.

2.50 QC

There was no COP that described the actions to be taken when a sterility test result was found to be positive and records of action taken in such a situation were not clear eg "Microbiology worksheet" 26 June 1994 was viewed. Donation 312799 (?group O check digit 8) was listed as "RCC to freeze" and was found to produce a positive result that subsequently was confirmed as *Bacillus* sp. Records available for scrutiny were not adequate ie

- > an internal memo of 28 June 1994 contained the donation number and donors name and stated that the Director's decision on the disposition of this donation would be forwarded.
- > an internal memo of 27 June 1994, addressed to the Director requested guidance on what action was to be taken with this donation. This memo carried an unsigned, undated comment in red ink stating "discard as per the Director". This was stated to be an oral directive. There was no clear record of this instruction being given or received.
- > the QA Specialist was not copied any information pertaining to this matter (see also 2.49, above, the

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sterility test on this donation would have been performed on a bleedline segment).

2.51 QC

A small incubator (#26) was used to incubate the sterility tests. The operating range for this was said to be 35°C-37°C. This item of equipment was on the temperature monitoring/alarm system. However, QC staff do not routinely check the temperature profiles and accepted that the temperature could go out of range eg over a weekend, without their knowledge. QC also indicated that crossmatch, who would respond to alarms out of hours, would not necessarily advise QC staff of an alarm event for this equipment.

2.52 QC

The worksheets for factor VIII assays were dated only on the front page. The system needs a format that can conclusively identify eg page "X" of "Y" and date.

2.53 Waste Disposal

- > the system for disposing of biological waste was not covered by a COP.
- > different areas of the Centre appeared to be using different waste vouchers eg Nursing and QC. The Central Administrator indicated that a memo had been issued over a year ago to harmonise the process across the Centre.
- > a number of waste vouchers eg B184 and B413 were incomplete (ie signatures were missing) but were filed as completed.
- > TD repeat reactive components were not autoclaved before sending for incineration. (BFI, North Dakota came on site to collect waste).

2.54 Autoclaving

- > there was no COP for the autoclaving process.
- > worksheets carried unauthorised/unsigned changes.
- > there was no adequate record of autoclave runs that linked details such as contents, checks that temperature, time and pressure were satisfactory, and the outcome of sterility tube checks (see below).
- > sterility tube results were not reported back from QC - "they'd let me know if there was a problem". It was proposed to change this reporting arrangement on the spot without considering the various documentation changes that would result.
- > the cork board on the wall contained a memo dated 23 August 1990, referring to failures to achieve sterility on autoclaving. The Centre Administrator indicated this

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had been obsolete for some time and removed it from the board. It was not known how/if this memo was to be stored.

2.55 Components

There was concern that the system for introducing changes to COPs was not fully controlled eg COP CP/107 "Flagged Units", effective 31 Jan 1994 was modified by revision and shows changes effective 16 Sept 1994 but the documents carried the same version number and superseded documents were not recalled when the 16 Sept 1994 revision was issued.

2.56 QA

There is no Centre policy on the date format to be used. Various formats were used eg month/DD/YY on donor medical declaration forms; DD/MM/YY for BLIS and it was stated by a member of staff that the format was MM/DD/YY.

2.57 QA

There was concern that the QA Specialist was not being copied into relevant documentation eg see Appendix 1, 1.1.8 (last bullet point) and this appendix, 2.50. Also, a memo from the Assistant Nursing Manager (19 Oct 1994) to Blood Collection Area staff re "Recording Total Protein Values" had not been cleared and controlled for issue by the QA Specialist.

At other times the QA Specialist was merely copied information that they should have been responsible for controlling and signing off eg (product recalls from National are copied to the Laboratory Manager, not QA Specialist).

2.58 Product Inventory

Stock of Energix-B Hepatitis B Vaccine was examined (lot #1233AA, exp "96 No"). There were 37 vials in stock, the inventory record held in the TD lab showed 36 vials.

Occasionally, corrections were made to stock totals (said generally to be due to arithmetic errors). There was no error log for this activity.

COMMENT

It was noted that platelet counts in random and single donor platelets were well above specification. If this is confirmed perhaps consideration should be given to reducing the number of random platelet units in a "therapeutic dose" (6 units at present).

*Martin Bruce
Alan Rane*

COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA
INTERNATIONAL INSPECTION TEAM AUDIT OF WINNIPEG CENTRE

31 OCTOBER - 03 NOVEMBER 1994

APPENDIX 3

INTERNATIONAL CHECKLIST

*Martin Givens
Belin Harr*

**COMMISSION OF INQUIRY ON THE BLOOD SYSTEM IN CANADA:
INTERNATIONAL AUDIT TEAM CRITICAL CONTROL POINT CHECKLIST**

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
1. DONOR SELECTION				
1. Is there an effective donor deferral procedure	UK; CDD; USFDA	✓		1.1. This includes a procedure for self exclusion.
2. Is there a register of donors with a history of repeat reactivity in mandatory microbiological screening tests?	USFDA; UK	✓		1.1.2. This is "live" on a computer database in the static clinic and by microfiche for mobiles updated monthly
2 Do donor assessment areas provide an adequate level of privacy? ie can waiting donors see the completed questionnaire or <u>overhear</u> verbal questions and answers?	CRCS; UK; ATGA; CRCS; WHO; USFDA; CDD	✓	✓	1.2 Donor interview areas are half glass partitioned on the three sides. At audit donors could see VDU screens. Young children were allowed into the interview room.
3 Are prospective donors provided with information on AIDS/high risk activities at each donation?	USFDA; UK; ATGA; CRCS; EC	✓		
4 Do donors acknowledge in writing at each donation that they have read and understood the "health check"/"fit to donate" criteria?	USFDA; UK	✓		2.1. This was said to be done and although checklist for training included these requirements at audit on the static clinic they were not being followed.
5 Are donors made aware that recipients experience risk from transfusion and are they, therefore, asked to report any illness developing subsequent to the donation?	UK; ATGA; CRCS; CDD	✓		2.3. Local procedure implemented to meet the National 01 Nov 94 deadline, but obviously caused problems of constraints of time.
2. PREPARATION FOR VENESECTION				
1 Are blood packs inspected before use to ensure they are: 1. in date?	EC ATGA; UK		✓	
2. free from defects?	ATGA; UK; EC		✓	
2 Is there a secure procedure to ensure that donor records, blood packs and sample tubes are correctly labelled at the time of donation?	UK; USFDA; EC; CRCS	✓		3.1. Not adequately. General procedure was to say "Hello Mr - , how are you today."
3 Is the procedure for arm preparation: 1. appropriate?	USFDA; UK; EC; ATGA; WHO; CDD	✓		3.2. But — there was no mandatory policy on the use of needleguards. Staff on the static clinic were observed <u>not</u> to be using these. A number of needlestick injuries were reported each year.
2. validated?			✓	3.4. Yes, but concerns were registered. Despite 2 checks in the clinic, a third check by admin recorded 93 errors since June 1994.
3. BLOOD COLLECTION				
1 Is the identity of the donor checked before venepuncture?	ATGA; EC; UK		✓	
2 If local anaesthetic is used, do the procedures for preparation and injection: 1. follow 'clean' procedures (aseptic)?	ATGA, EC	N/A		
2. explicitly exclude resheathing of needles?		N/A		
3. avoid any chance of donor/donor cross infection?	ATGA	N/A		
3 Are the donor attendant duties organised so as to prevent any mix up in documentation, samples or labelling between donors/donations?		✓		
4 Is the donation number checked on all items to ensure that those on the blood packs and sample tubes are identical with those on the paper work?	EC; UK	✓	✗	

COMMENTS - IDENTIFY BY NUMBER

N/A = Not applicable.

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Are any excess labels defaced/destroyed immediately after labelling is complete?			✓	3.5. Multiple Copies of the unique donation number are returned to the Centre and used in various applications. At audit this was identified as a serious GMP label defect due to detached labels sticking to the wrong pack. i.e. packs had 2 donation numbers. At the wrap-up meeting it was confirmed that this also was a problem for hospitals.
6 Once the donation is complete is there a procedure that requires the container, samples and documentation, especially labels, to be checked for defects?	EC; USFDA	✓		3.6. — not a documented procedure but see comments for 3.4.
7 Adverse Donor Events 1. Is there a written procedure for resuscitation?	WHO; CDD	✓		3.7.2. There is no record of CPR training for physicians. all CPR first aid records for other staff is past review date.
2. Are staff trained and annually updated in resuscitation techniques?	WHO	✓	✓	4.1 Procedure not written but is secure.
3. Is there a written procedure that requires the components of the resuscitation "kit" to be checked on a regular schedule and logged?		✓		4.4 Positive sample I.D. is lost at time of preparing samples to send to National for confirmatory testing.
4. TRANSFUSION MICROBIOLOGY				4.5 Check digit must be entered.
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA	✓		4.6 For HCV to repeat testing - use CAVRO.
2 Are tests performed on samples taken at the time of donation?	WHO; USFDA; CDD	✓		4.7 Samples for lot approval of every kit rec'd from National except for anti-HCV - received directly from Ortho.
3 Are reagents used as recommended by the manufacturer?	USFDA; UK; CDD	✓		4.9.2. But this is in the form of a training manual.
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA	✓	✓	4.10 Yes, plus computer control
5 Is there a secure system for keyboard entry of numbers?		✓		
6 Are samples ever manually added to test wells? If yes, describe the circumstances and procedures.		✓		
7 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes: manufacturers? in-house? licensing/national authority? how frequently tested?	UK; ATGA; USFDA; EC	✓	✓	
8 Is a system of positive reporting used? (ie are results recorded for all samples)	UK	✓		
9 1. If results are interpreted by computer software, is this validated?	CRCS; UK	✓		
2. If results are interpreted manually, is this governed by a written procedure?	UK	✓		
10 For initial screening test positives and previously recorded positives, is there a secure procedure for ensuring that the correct samples are retrieved for repeat testing?	UK	✓		
11 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS	✓		
12 Are there secure, written procedures that permit the identification of all subcomponents of a donation and ensure their retrieval, disinfection and disposal?	UK; CRCS; USFDA; WHO	✓		

COMMENTS - IDENTIFY BY NUMBER

(not seen in Montreal or Saint John).

General comments - Winnipeg seem to make more use of the computer system. eg. have online access to donor database in static clinic and in various applications in the TD Lab (see 4.10).

Also noted that pre acceptance testing of TD kits was done on every consignment rather than every lot. (unlike Montreal & Saint John)

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
13 For components in long term storage, is there a secure procedure for storage, retrieval, testing and reporting of archive samples?				4.13. Winnipeg store archive donor samples off site but there was insufficient time to explore further.
14 Are test data reviewed by personnel before final results are reported?	USFDA; UK	✓		
15 Do repeat reactive results produce a rapid deferral flag in the donor record?	UK	✓		4.16. Not written as per a Col
16 If confirmatory testing of positives is performed off site, is there a secure, written procedure for preparing and labelling samples?			✓	4.18 But is done for anti-HCV repeat reactive.
17 Is there a secure, written procedure for inputting and editing donor files on receipt of confirmatory test results.		✓		5.1 Procedure is ^{not} written but is secure.
18 For HBsAg and anti-HIV 1 + 2 repeat reactives, is there a written procedure to ensure that any previously prepared component still held in inventory is quarantined?	USFDA		✓	5.3. Reagents are diluted. Some minor improvements in records of the process were possible.
5. BLOOD GROUPING (ABO & RhD)				
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA	✓		5.4 For manual blood groups, samples are given a sample reference number to link item to the donation number but seems OK!
2 Are tests performed on samples taken at the time of donation?	USFDA; WHO	✓		
3 Are reagents used as recommended by the manufacturer?	USFDA		✓	5.5. Reagents checkdigit but not double entry.
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA		✓	5.6. Control red blood cells are used for ABO and Rh D grouping, they are obtained from whole blood donations and are tested at the end of each series of samples.
5 Is there a secure system for keyboard entry of numbers?		✓		
6 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes, describe: controls used their source how frequently tested	UK; ATGA; USFDA		✓	
7 1 If results are interpreted by computer software, is this validated?	CRCS	✓		
2 If results are interpreted manually, is this governed by a written procedure?		✓		
8 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS	✓		
9 Are test data reviewed by personnel before final results are reported?	USFDA; UK	✓		
6. COMPONENT PREPARATION				
1 Is there a procedure that ensures a rapid and effective reconciliation of all components at all stages of their manufacture?		✓		

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
2 If an open processing system is used; 1. is component sterility testing performed?	UK	✓		6.2 Yes, but component open processing is a major problem area.
2. is environmental monitoring performed, especially during the open procedure?	UK		✓	
3 If a sterile connecting device is used 1. is the system validated?	UK	N/A		6.4.2 Improvements were required. eg. frozen red cells at -65°C labels with indelible marker pen were coming off.
2. what is the validation interval?		N/A		
4 Where component preparation requires relabelling of a pack eg for washed red cells or for pooled platelets 1. is this governed by a written procedure?	UK	✓		7.1 Secure, but involves much manual transcription.
2. is the procedure secure?	UK		✓	
7. COMPONENT LABELLING & RELEASE TO STOCK				
1 Do procedures ensure that components cannot be released to stock until all the required tests (mandatory and additional) have been completed, and records reviewed, with satisfactory outcomes?	UK; USFDA	✓		8.2 New clean system installed April 94 - not since checked (schedule was six monthly)
2 Is the procedure for labelling blood components? 1. a written procedure	USFDA	✓		At Users of system were unsure of its functionality - no cop.
2. secure?		✓		
3. followed?		✓		
3 In exceptional instances are components issued when they do not conform to mandatory requirements (eg test results not available). If yes, is this governed by a written, secure procedure?	UK; USFDA	N.P.		8.2 Some critical equipment was not on the emergency power supply and walk-in freezer & coldrooms had only one compressor (no space for backup)
4 Are blood components ever received from non-Red Cross blood collection facilities? If yes, is this covered by a written, secure procedure?	CRCS	N.P.		
8. COMPONENT STORAGE				
1 Do blood component storage areas and procedures allow for appropriate segregation and effective identification of components of different status eg 1. untested	UK, CRCS EC; USFDA; CDD	✓		
2. "hold" status		✓		
3. Biohazard		✓		
4. available for issue		✓		
2 Are arrangements for monitoring the temperature of blood component storage areas adequate?	CRCS; UK; CDD	✓	✗	
3 Are monitoring systems and alarms regularly validated to ensure functionality.	EC; UK			✓

COMMENTS - IDENTIFY BY NUMBER

N/A - Not applicable.

N.P. - Not Pursued.

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
9. INFORMATION TECHNOLOGY				
1 Has the computer system been validated to provide assurance that the system operates properly in the intended environment? If yes, is this documented?	USFDA; ATGA USFDA	✓ ✓		9.1 Source code for BIS is held at National. They undertake all validation / change control etc.
Are all changes and modifications that are made to the computer system evaluated to assure that no other areas of the system are adversely affected by the change?	USFDA; CDD		✓	9.3. Users manual from National not adequate. Locally produced manual does not cover all areas of application.
2 Did the validation reflect normal, stress, exceptional, boundary and invalid conditions?	USFDA		✓	
3 Is the computer system covered by an appropriate users manual?	CRCS; ATGA; EC; USFDA; CDD		✓	9.4. Only explored from for computing staff - probably adequate but not documented.
4 Are users of the system given adequate training?	CRCS; USFDA	✓		9.5. No password change control labely but no notification from National - no enquiry to National.
5 Does the system have security procedures to prevent unauthorised access?	USFDA; ATGA; CDD; CRCS; EC		✓	(Montreal and Saint John were aware that p mandate password change had been discontinued by National)
6 Is an audit trail maintained so that all changes made to the data can be traced?	ATGA; USFDA		✓	9.6 The computer room staff did not know which functions / data entry points had an audit trail - except for donor / donation linking but changes due to initial errors (noted by checking) are not logged.
7 Is there a procedure for reporting problems with the system?	USFDA; CRCS		✓	9.7. No written procedure, phone not fax to hot line but are given a reference number.
8 Are written change control procedures available and effective?	USFDA; ATGA; EC	See 9.1		9.9 Procedure has never been trialled.
9 Are there recovery procedures to return the system to its previously operating state without loss of function, reliability, data or memory?	ATGA; EC		✓	10.1 Appropriate training programmes are now being developed but there is no overview/co-ordination
10 Is barcode quality/readability monitored?			✓	10.2. Plans for annual review
10. TRAINING				
1 Do employees have appropriate education, training and experience?	USFDA; EC; CRCS; WHO; UK; CDD	✓		
2 Does the training programme include an annual performance review and identification of training needs?	CRCS; CDD		✓	
3 Is employee training documented?	CRCS; UK; CDD	✓		
11. QUALITY ASSURANCE				
1 Is there an individual responsible to management for quality who is independent of production/manufacturing?		✓	MB	
2 Does this individual have sufficient authority to function effectively?	EC, ATGA		✓	
3 Is there a system to control the review, issue, use, retrieval and storage of documents?	UK; CDD		✓	
4 Is there a programme of self inspections (audits).	EC, UK; CDD		✓	

COMMENTS - IDENTIFY BY NUMBER are in hand and some progress is being made with error reports to identify training needs but this is at an early stage of development.

11.2 No, this individual does not have sufficient authority (a knowledge / training / experience to function effectively as QA Manager within a system of GMP.

11.3 There is a system under development but this is under review and is not adequately developed.

11.4. Some audits have taken place but there is no formal policy or plan.

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Is there a procedure to ensure that new equipment, tests or procedures are validated 1. before being introduced for routine use?	EC CDD		✓	11.5.4. This was noted to be a problem area that required attention.
2. After repairs or readjustments which may affect performance.			N/A	
3. If any problems are suspected.			N/A	11.6. No local COPs for recall of fractionated or fresh blood components. A problem was recorded at audit with a "recall" event on Immuno factor TS. - 1x One vial not accounted for, not noted or investigated.
4. Does the procedure include the production of a validation report that indicates authorisation is given to introduce (or not) this new piece of equipment/test/procedure, the date of authorisation and the date of introduction?			✓	
6 1. Is there an effective, written procedure/s for product recall?	UK		✓	11.9. There was no GMP systems approach for frozen/thawed or washed red cells. (open processing in a poor environment with poor procedures)
2. Do the recall procedure/s apply to fresh blood components and fractionated products.			N/A	
3. How often has the procedure been used in the last 12 months for blood components? fractionated products?		N.P.		
7 Is there an effective, written procedure for reporting adverse reactions to fractionated products, blood components?	CDD; USFDA		✓	
8 Is adequate provision made to support these adverse reaction/recall procedures out of normal working hours?		✓		
9 Is there a consistent approach to GMP (across all component/product types and processes)?			✓	

COMMENTS - IDENTIFY BY NUMBER

N/A = NOT APPLICABLE.

N.P. = NOT PURSUED

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
1. DONOR SELECTION				
1. Is there an effective donor deferral procedure	UK; CDD; USFDA			
2. Is there a register of donors with a history of repeat reactivity in mandatory microbiological screening tests?	USFDA; UK			
2 Do donor assessment areas provide an adequate level of privacy? ie can waiting donors see the completed questionnaire or overhear verbal questions and answers?	CRCS; UK; ATGA; CRCS; WHO; USFDA; CDD			
3 Are prospective donors provided with information on AIDS/high risk activities at each donation?	USFDA; UK; ATGA; CRCS; EC			
4 Do donors acknowledge in writing at each donation that they have read and understood the "health check"/"fit to donate" criteria?	USFDA; UK			
5 Are donors made aware that recipients experience risk from transfusion and are they, therefore, asked to report any illness developing subsequent to the donation?	UK; ATGA; CRCS; CDD			
2. PREPARATION FOR VENESECTION				
1 Are blood packs inspected before use to ensure they are: 1. in date?	EC ATGA; UK			
2. free from defects?	ATGA; UK; EC			
2 Is there a secure procedure to ensure that donor records, blood packs and sample tubes are correctly labelled at the time of donation?	UK; USFDA; EC; CRCS			
3 Is the procedure for arm preparation: 1. appropriate?	USFDA; UK; EC; ATGA; WHO; CDD			
2. validated?				
3. BLOOD COLLECTION				
1 Is the identity of the donor checked before venepuncture?	ATGA; EC; UK			
2 If local anaesthetic is used, do the procedures for preparation and injection: 1. follow 'clean' procedures (aseptic)?	ATGA, EC			
2. explicitly exclude resheathing of needles?				
3. avoid any chance of donor/donor cross infection?	ATGA			
3 Are the donor attendant duties organised so as to prevent any mix up in documentation, samples or labelling between donors/donations?				
4 Is the donation number checked on all items to ensure that those on the blood packs and sample tubes are identical with those on the paper work?	EC; UK			

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Are any excess labels defaced/destroyed immediately after labelling is complete?				
6 Once the donation is complete is there a procedure that requires the container, samples and documentation, especially labels, to be checked for defects?	EC; USFDA			
7 Adverse Donor Events 1. Is there a written procedure for resuscitation?	WHO; CDD			
2. Are staff trained and annually updated in resuscitation techniques?	WHO			
3. Is there a written procedure that requires the components of the resuscitation "kit" to be checked on a regular schedule and logged?				
4. TRANSFUSION MICROBIOLOGY				
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA			
2 Are tests performed on samples taken at the time of donation?	WHO; USFDA; CDD			
3 Are reagents used as recommended by the manufacturer?	USFDA; UK; CDD			
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA			
5 Is there a secure system for keyboard entry of numbers?				
6 Are samples ever manually added to test wells? If yes, describe the circumstances and procedures.				
7 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes: manufacturers? in-house? licensing/national authority? how frequently tested?	UK; ATGA; USFDA; EC			
8 Is a system of positive reporting used? (ie are results recorded for all samples)	UK			
9 1. If results are interpreted by computer software, is this validated?	CRCS; UK			
2. If results are interpreted manually, is this governed by a written procedure?	UK			
10 For initial screening test positives and previously recorded positives, is there a secure procedure for ensuring that the correct samples are retrieved for repeat testing?	UK			
11 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS			
12 Are there secure, written procedures that permit the identification of all subcomponents of a donation and ensure their retrieval, disinfection and disposal?	UK; CRCS; USFDA; WHO			

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
13 For components in long term storage, is there a secure procedure for storage, retrieval, testing and reporting of archive samples?				
14 Are test data reviewed by personnel before final results are reported?	USFDA; UK			
15 Do repeat reactive results produce a rapid deferral flag in the donor record?	UK			
16 If confirmatory testing of positives is performed off site, is there a secure, written procedure for preparing and labelling samples?				
17 Is there a secure, written procedure for inputting and editing donor files on receipt of confirmatory test results.				
18 For HBsAg and anti-HIV 1 + 2 repeat reactives, is there a written procedure to ensure that any previously prepared component still held in inventory is quarantined?	USFDA			
5: BLOOD GROUPING (ABO & RhD)				
1 Is there a secure, written procedure for reconciling donations collected with samples received for testing?	USFDA			
2 Are tests performed on samples taken at the time of donation?	USFDA; WHO			
3 Are reagents used as recommended by the manufacturer?	USFDA			
4 Are samples positively identified at all stages of the test procedure? If no, describe manual procedures/assess their security.	CRCS; UK; USFDA			
5 Is there a secure system for keyboard entry of numbers?				
6 Are appropriate control samples used to confirm satisfactory performance of the test before results are accepted? If yes, describe: controls used their source how frequently tested	UK; ATGA; USFDA			
7 1 If results are interpreted by computer software, is this validated?	CRCS			
2 If results are interpreted manually, is this governed by a written procedure?				
8 Is there a secure, written procedure for manual editing of the result status following repeat testing?	UK; CRCS			
9 Are test data reviewed by personnel before final results are reported?	USFDA; UK			
6: COMPONENT PREPARATION				
1 Is there a procedure that ensures a rapid and effective reconciliation of all components at all stages of their manufacture?				

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
2 If an open processing system is used; 1. is component sterility testing performed?	UK			
2. is environmental monitoring performed, especially during the open procedure?	UK			
3 If a sterile connecting device is used 1. is the system validated?	UK			
2. what is the validation interval?				
4 Where component preparation requires relabelling of a pack eg for washed red cells or for pooled platelets 1. is this governed by a written procedure?	UK			
2. is the procedure secure?	UK			
7. COMPONENT LABELLING & RELEASE TO STOCK				
1 Do procedures ensure that components cannot be released to stock until all the required tests (mandatory and additional) have been completed, and records reviewed, with satisfactory outcomes?	UK; USFDA			
2 Is the procedure for labelling blood components? 1. a written procedure	USFDA			
2. secure?				
3. followed?				
3 In exceptional instances are components issued when they do not conform to mandatory requirements (eg test results not available). If yes, is this governed by a written, secure procedure?	UK; USFDA			
4 Are blood components ever received from non-Red Cross blood collection facilities? If yes, is this covered by a written, secure procedure?	CRCS			
8. COMPONENT STORAGE				
1 Do blood component storage areas and procedures allow for appropriate segregation and effective identification of components of different status eg 1. untested	UK, CRCS EC; USFDA; CDD			
2. "hold" status				
3. Biohazard				
4. available for issue				
2 Are arrangements for monitoring the temperature of blood component storage areas adequate?	CRCS; UK; CDD			
3 Are monitoring systems and alarms regularly validated to ensure functionality.	EC; UK			

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
9. INFORMATION TECHNOLOGY				
1 Has the computer system been validated to provide assurance that the system operates properly in the intended environment? If yes, is this documented?	USFDA; ATGA USFDA			
Are all changes and modifications that are made to the computer system evaluated to assure that no other areas of the system are adversely affected by the change?	USFDA; CDD			
2 Did the validation reflect normal, stress, exceptional, boundary and invalid conditions?	USFDA			
3 Is the computer system covered by an appropriate users manual?	CRCS; ATGA; EC; USFDA; CDD			
4 Are users of the system given adequate training?	CRCS; USFDA			
5 Does the system have security procedures to prevent unauthorised access?	USFDA; ATGA; CDD; CRCS; EC			
6 Is an audit trail maintained so that all changes made to the data can be traced?	ATGA; USFDA			
7 Is there a procedure for reporting problems with the system?	USFDA; CRCS			
8 Are written change control procedures available and effective?	USFDA; ATGA; EC			
9 Are there recovery procedures to return the system to its previously operating state without loss of function, reliability, data or memory?	ATGA; EC			
10 Is barcode quality/readability monitored?				
10. TRAINING				
1 Do employees have appropriate education, training and experience?	USFDA; EC; CRCS; WHO; UK; CDD			
2 Does the training programme include an annual performance review and identification of training needs?	CRCS; CDD			
3 Is employee training documented?	CRCS; UK; CDD			
11. QUALITY ASSURANCE				
1 Is there an individual responsible to management for quality who is independent of production/manufacturing?				
2 Does this individual have sufficient authority to function effectively?	EC, ATGA			
3 Is there a system to control the review, issue, use, retrieval and storage of documents?	UK; CDD			
4 Is there a programme of self inspections (audits).	EC, UK; CDD			

COMMENTS - IDENTIFY BY NUMBER

ITEM	REFERENCE	YES	NO	COMMENTS - IDENTIFY BY NUMBER
5 Is there a procedure to ensure that new equipment, tests or procedures are validated 1. before being introduced for routine use?	EC CDD			
2. After repairs or readjustments which may affect performance.				
3. If any problems are suspected.				
4. Does the procedure include the production of a validation report that indicates authorisation is given to introduce (or not) this new piece of equipment/test/procedure, the date of authorisation and the date of introduction?				
6 1. Is there an effective, written procedure/s for product recall?	UK			
2. Do the recall procedure/s apply to fresh blood components and fractionated products.				
3. How often has the procedure been used in the last 12 months for: blood components? fractionated products?				
7 Is there an effective, written procedure for reporting adverse reactions to fractionated products, blood components?	CDD; USFDA			
8 Is adequate provision made to support these adverse reaction/recall procedures out of normal working hours?				
9 Is there a consistent approach to GMP (across all component/product types and processes)?				

COMMENTS - IDENTIFY BY NUMBER

APPENDIX VI E

The committee, concerned that aspects of process controls and management issues would be missed with very specific checklists, drafted the following questions for the inspectors. The purpose of the questions is to strike a balance between specifics and process control and management issues.

- 1 Describe the system for change control of manufacturing processes (SOP's, donor screening, viral testing, and the like). Is the system used? Please provide documentation of the last three manufacturing process changes implemented and their validation.
- 2 Describe the system of error reporting and management. Is the system a component of continuous improvement? Provide error management reports for the 30 days 6 months ago. Provide documentation of three recent improvements made in processes and their validation.
- 3 Describe the system to identify personnel who need additional training in manufacturing processes (donor recruiting, screening and drawing, viral testing, labelling, and the like). Provide the documentation of the last retraining episode.
- 4 Describe the system to evaluate the quality and adequacy of services provided to customers. How is that information used?
- 5 Describe the system to respond to deficiencies found during audits. Provide documentation of validation of corrective actions of adverse audit findings.
- 6 Describe local initiatives that you think (could) would have improved the safety of the blood supply in your region. Have any of them been implemented?
- 7 Describe the involvement of senior management with cGMP and process control issues. Provide documentation of this involvement (attendance at QA meeting, review of error, management, and the like).
- 8 Describe the major changes in the system(s) planned for your centre over the next 2 years. Do you have the resources to implement the changes safely?

SAFETY OF BLOOD TRANSFUSION WITH RESPECT TO HIV

In considering the safety of blood transfusion with respect to HIV transmission, there are a number of perspectives from which this can be approached. From the perspective of the attending physician ordering a transfusion and the perspective of the recipient, the parameter of interest is the probability that a given unit of blood is infectious. From the perspective of the blood system as a whole, another important parameter is the number of individuals who will become HIV infected as a result of a blood transfusion. This is influenced by the distribution of the numbers of units received per recipient and the infectivity. When the number of infected units is small and the number of recipients is large, the number of infected recipients is the number of infected units times the infectivity rate since the probability of a single recipient receiving more than one infected unit is virtually zero. From the point of view of public health and society as a whole, it might be the number of individuals who not only become HIV infected as a result of a transfusion, but also survive the underlying condition that necessitated the transfusion. We focus our consideration on the probability that infectious units will escape detection in the blood supply.

An infectious unit of blood may be released by the supplier essentially as a result of one of three mechanisms. First, the donor may have only recently been infected with HIV (denoted an incident infection) and antibodies may not yet have reached detectable levels. This is commonly referred to as "the window period" and is inherent in the current antibody detection technology available. We have termed this a group I error.

The second mechanism occurs due to failure of the test to detect units of blood donated by individuals with established HIV infection (denoted prevalent infections). Such failures are commonly known as false negatives and occur whenever a test has less than 100 % sensitivity. We have termed these group II errors.

The third mechanism occurs due to failure of the system to remove detected units of blood donated by individuals with established HIV infection. Such system failures might occur as a result of a combination of system errors (transcription error, mislabelling error, etc) which results in an infectious unit failing to be removed from the supply. We have called this a group III error.

In order to estimate infectivity rates in the Canadian blood supply, we conducted Monte Carlo simulations. In order to describe these, we first define and discuss a number of key parameters.

P = the prevalence of established/detectable HIV infection per 100,000 blood donations;

P is best estimated by HIV infection rates reported by the Red

Cross from recent years although the true number of prevalent cases is trivially higher by virtue of the small number of system detection failures (see below).

In the simulation, **P** was distributed with a mean of 2.0 per 100,000 and a 95% confidence interval of (1.16, 2.82). This was based on Red Cross data¹ for the period April 1993 to March 1994 in which 23 of 1,154,501 donations were confirmed positive.

N = the number of units donated and transfused in a year;

The number of red cell units transfused each year has been declining. Red Cross projections place the number likely to be transfused in 1995 in the range of 713,000 to 761,000. In the simulation, **N** was therefore set to be 750,000.

I = the incidence of HIV infection per 100,000 repeat donors per year;

This parameter is restricted to repeat donors since it is only in this group that the incidence rate can be estimated from blood donor studies. In Canada, a study of repeat donors in Quebec² found an incidence rate of 4.1 per 100,000 person-years. This estimate is somewhat higher than that observed among repeat blood donors in the R.E.D.S. study in the U.S. of 2.6 per 100,000 person-years and may be higher than incidence rates among blood donors in the rest of Canada. In the simulation, **I** was taken to be log normally distributed with a mean rate of 4.1 per 100,000 and a standard deviation of 2.1 based on the Quebec data. NOTE: This, along with the window period below, are by far the most important parameters in determining the probability of an infected unit of blood escaping detection. The use of the high rate from the Quebec study for this parameter may lead to an overestimate.

f = the fraction of all blood donations which are derived from donors who are donating for the first time;

During the period April 1993 to March 1994, first time donations represented

¹ Gill P. Personal communication, July 1994.

² R.S. Remis and G. Delage, "Estimation of HIV Incidence Among Repeat Blood Donors in Montreal: A Pilot Study," Presented at IXth International Conference on AIDS, Berlin, June 1993; Abstract P0-C21-3111.

about 11% of all donations.³ For the simulation, f was taken to be normally distributed with a mean of 11% and a standard deviation of 2%.

R = the relative risk of HIV incidence among first time donors relative to repeat donors;

R cannot be directly estimated since the incidence among first time donors is not easily measured. However, one can use the relative prevalence rate as a proxy. During the period April 1993 to March 1994, first time donations had a prevalence of 8.0 per 100,000 compared to 1.3 per 100,000 among repeat donations.⁴ However, the prevalence among repeat donations is not equivalent to the prevalence among repeat donors since multiple donations are often received from the same repeat donor during a given year. Given an estimate of around 2 repeat donations per year yields a relative prevalence of 3.1 for repeat donors relative to first time donors. Based on this, in the simulation, R was log normally distributed with a mean of 3.1 and a standard deviation of 0.67.

S = the detection rate;

In this instance S , or its complement ($1-S$), the detection failure rate, is meant to incorporate not only false negatives as a result of the test algorithm (group II errors), but also system failures such as mislabelling, transcription errors, misreading, etc (group III errors). In an editorial regarding kit and laboratory performance in HIV testing, Zuck⁵ utilized a detection rate of .998 based on a proficiency study by Cross et al.⁶ For this simulation, we utilized a detection rate of .998 with a 95% confidence interval of (.9968, .9992).

w = the duration of the window period measured in days;

The window period can be estimated from published studies. A collaborative

³ Gill, P. Personal communication, July 1994.

⁴ Gill, P. Personal communication, July 1994.

⁵ T.F. Zuck, "HIV-1 Testing: Implications of Kit and Laboratory Performance. *Arch Pathol Lab Med* 116 (1992): 482-3.

⁶ G.D. Cross, et al. "Analytic Sensitivity and Specificity of Enzyme Immunoassay Results in Testing for HIV-1 Antibody," *Arch Pathol Lab Med* 116 (1992): 477-81.

CDC study⁷ which modelled data from previous recipients of blood from 179 seroconverting blood donors prior to 1991, and derived a window period estimate of 45 days (95% CI: 34 - 55). This was based on earlier generations of EIA tests. Subsequently, Busch et al⁸ studied pre-seroconversion specimens from 81 seroconverters using 3rd generation anti-HIV-1/HIV-2 enzyme immunoassays and estimated that the mean window period had fallen 19.7 days (95% CI: 7.7 - 31.6) relative to enzyme immunoassays used prior to 1990. Combining these data gives rise to an estimate of a mean window period for 3rd generation anti-HIV-1/HIV-2 enzyme immunoassays of 25.4 days (95% CI: 9.8, 40.7). The latter data were used in the Monte Carlo simulation.

$w' = (w/365)$ or the duration of the window period in years.

Results

Given the above parameters, the number of units that would escape detection and might be transfused in Canada annually is given by the expression:

$$number = \frac{(1-S) \cdot P \cdot N + I \cdot w' \cdot N \cdot (R \cdot f + (1-f))}{100,000}$$

We ran 10,000 simulations in which the parameters were allowed to follow the distributions described above. The number of infected units ranges from 0 to 6 with a mean of 2.7 and a median of 3.0. The precise distribution is given in the table below:

Number of Infected Units	Likelihood of Occurrence
0	0.7%
1	12.4%
2	36.9%
3	30.3%
4	13.4%
5	4.6%
6	1.8%

⁷ L.R. Peterson, et al, "Duration of Time from HIV-1 Infectiousness to Development of Detectable Antibody," *Transfusion* 1994; In press.

⁸ M.P. Busch, et al, "Time Course of Detection of Viral and Serological Markers Preceding HIV-1 Seroconversion." *Ann Int Med* 1994; In press.

Thus, we can conclude that, under the parameter assumptions above, approximately 1 to 4 units of HIV infected blood will escape detection in Canada in 1995. Further, the likelihood is about 93% that the number of units escaping detection will be in the interval of 1 to 4. When measured as a risk per unit of transfused blood, the expected risk is 1 in 282,000 units with a 93% confidence interval ranging from 1 in 750,000 to 1 in 188,000.

As the probability of a single individual receiving 2 different infected components is virtually zero, then we may make the same inferences about the number of persons receiving infected blood. Given that each donation can give rise to 3 components (red cells, plasma, and platelets), the number of different persons receiving infected components would likely be in the range of 1 to 12.

The simulation confirmed what can be inferred from consideration of the above equation. That is that the 4 most important variables in determining risk of HIV transmission (in descending order based on rank correlation) are:

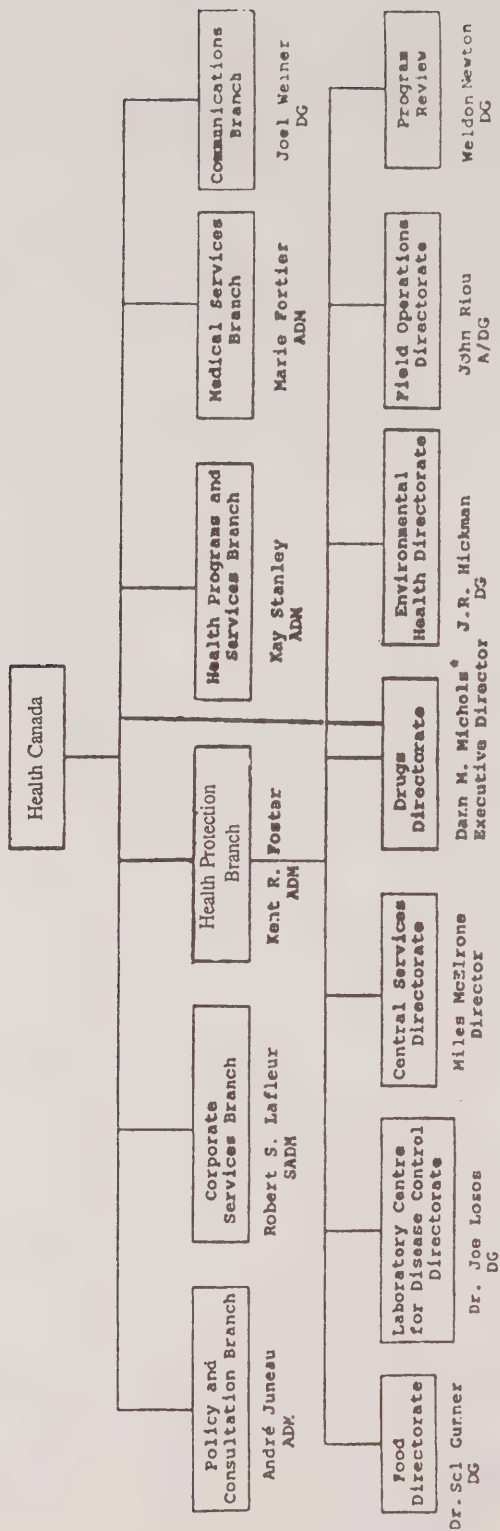
1. duration of the window period (0.67)
2. HIV incidence among repeat donors (0.55)
3. relative risk for first-time donors (0.11)
4. proportion of first-time donors (0.08)

It also demonstrates that the prevalent cases of HIV infection among blood donors and system insensitivity in detecting and removing them contribute little to HIV transmission compared with infectious units in the window period. Put another way, virtually all of the residual risk of HIV in the blood supply is due to group I error, and virtually none is due to group II and group III error.

APPENDIX VIII

ORGANIZATIONAL CHARTS OF HEALTH CANADA

ORGANIZATION CHART

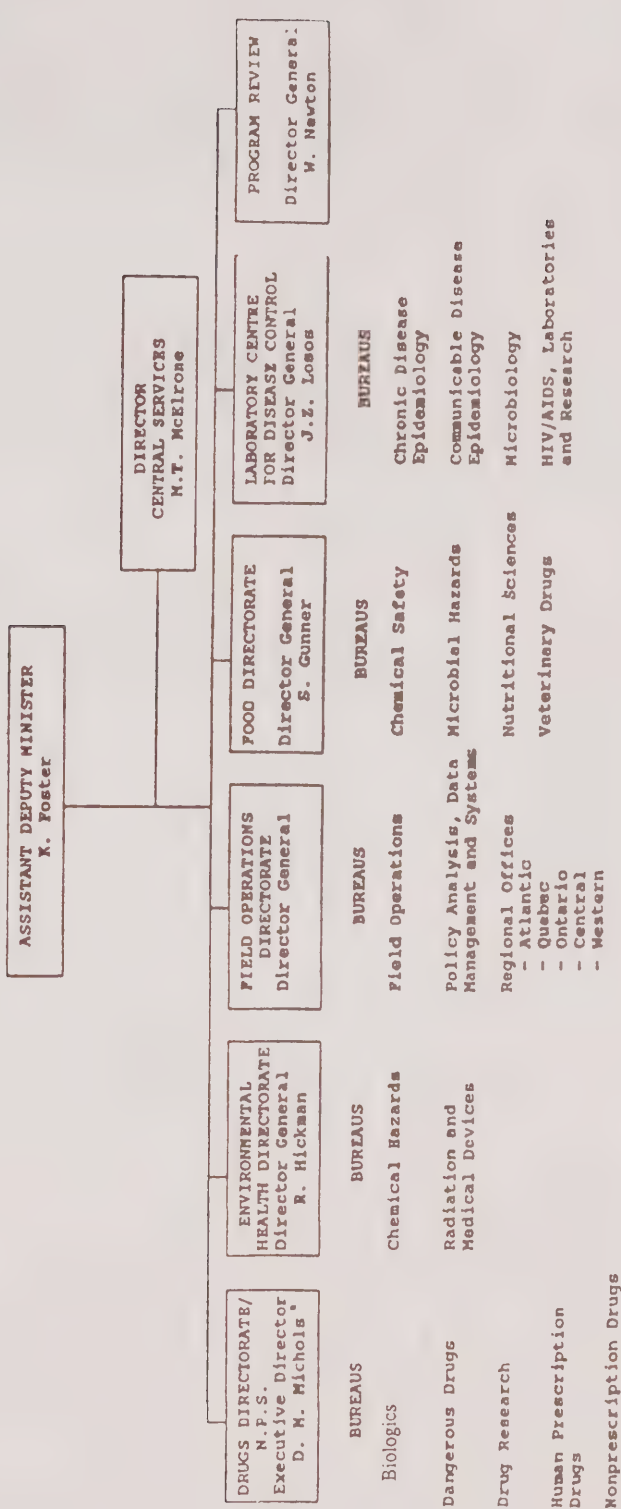


* (Mr. Michols is an ADM responsible to the Deputy Minister, managing the Drugs Directorate on assignment).

February 1994

HEALTH PROTECTION BRANCH

February 1, 1984



* (Mr. Nichols is an ADM responsible to the Deputy Minister, managing the Drugs Directorate on assignment.)

September 6, 1994

RELATIONSHIP CHART

EXECUTIVE DIRECTOR
NATIONAL PHARMACEUTICAL
STRATEGY / DRUGS DIRECTORATE
D. Michols

Renewal Office (B. Penning) — Chief Administrative Officer (D.P. Mills)
Professional Development Coordinator (K. Kirk) — Communications Officer (G. Lauriault)

Bureau of Biologics	Bureau of Drug Surveillance	Chemistry & Manufacturing	Bureau of Drug Research	Bureau of Human Prescription Drugs	Bureau of Nonprescription Drugs	Policy and Regulatory Affairs
K. Bailey	L.B. Rowse	P. Jeffs	G. Mattok (A)	C. Franklin	M. Carman	D. Spac
<u>Divisions</u>	<u>Divisions</u>		<u>Divisions</u>	<u>Divisions</u>	<u>Divisions</u>	<u>Divisions</u>
Bacterial Products	Domestic Control	Pharmaceutical Evaluation	Biopharmaceutics & Pharmacodynamics	AIDS & Viral Diseases	Drug Evaluation	Biometrics & Computer Sciences
Blood Products	Regional Liaison	Biopharmaceutics Evaluation	Life Sciences	Cardio-Vascular	Pharmaceutical Assessment and Cosmetics	Drug Regulatory Affairs
Viral Products	Information Services		Pharmaceutical Chemistry	Central Nervous System	Product Regulation	National Pharmaceutical Strategy
Compliance	Administration			Endocrinology, Metabolism and Allergy	Biopharmaceutics Evaluation	Submission & Information
	International Control and Licencing			Gastro-Enterology, Hematology, Oncology		
	GMP & Quality Assurance			Infection and Immunology		
	Adverse Drug Reaction Monitoring			Appraisal & Info. Management		

The review of CISCO was conducted by Committee Members Dr. Thomas Zuck, Dr. Martin Schechter, Paul Lavoie, and two outside consultants, Ms. Jude Tessel of the Hoxworth Blood Centre in Cincinnati, and Ms. Sherri Canjar of Confederation Life in Toronto.

CISCO REVIEW

Description of CISCO

CISCO is an Oracle-based (relational database) blood center data management system that is stated to be in the final stages of development, testing and validation. Because of the state of development, many FDA and cGMP requirements are incompletely developed. The system runs on a RS 6000 (IBM) and it is anticipated that one will be placed in each of the 17 donor centers currently operating in Canada. A subsystem can be deployed to mobile clinics that links the mobile data handling to that of the Centre and the national data real-time sharing.

Overall Impression

Much of the system continues to be in development; however, no major defect was observed that would make the system unsuitable for deployment within the CRC Blood System, **except** the lack of a laboratory module (the ability to link donor testing results to the rest of the database electronically) and the length of time needed to deploy the system. It is not possible to predict its approval or acceptance by the American FDA; the system appears to have significant shortfalls when measured against the FDA computer validation guidelines recently published. Despite this overall impression that the system would be useful, several comments are offered with the intent of being helpful.

Functionality

- the donor registration and screening process are labour intensive
- subroutine windows appear in various places on the main screens - may result in suboptimal compliance
- the duplicate donor record problem could be strengthened
 - Soundex is not an especially robust program
 - prompt strategy is relatively weak
 - no method to assure compliance with prompt query
- the reasons for donor deferrals are available to many staff
 - these data should be protected by a high level security code
 - only staff with a compelling need to know should have access
- it is unclear whether the method for stress testing, training, etc, via the Ottawa mainframe will be acceptable to the FDA
- it is unclear what training will be the responsibility of ETCOM and what will be the responsibility for the centres and national CSR.

- it is unclear what training will be the responsibility of ETCOM and what will be the responsibility for the centres and national CSR.
 - many training materials are incomplete at this time
 - strategy for training could not be evaluated completely
- query of donations at other sites is user driven rather than machine generated
- need equipment identification for batch record - 128 may be here
- the negative fill option for manual test results should not be permitted
- some of the requirements of Figure 8 - archiving and the like are undeveloped

APPENDIX X

BLOOD CENTRE DIAGRAM*

* Provided by Dr. Thomas F. Zuck.

BLOOD SYSTEM SEVEN PRINCIPLES

1. The voluntary donor system should be maintained and protected.
2. National self-sufficiency in blood and plasma collections should be encouraged.
3. Adequacy and security of supply of all needed blood, components and plasma fractions for Canadians should be encouraged.
4. Safety of all blood, components and plasma fractions should be paramount.
5. Gratuities of all blood, components and plasma fractions to recipients within the insured health services of Canada should be maintained.
6. A cost-effective and cost-efficient blood system for Canadians should be encouraged.
7. A National Blood Program should be maintained.

CRITICAL CONTROL POINTS

1. ORGANIZATIONAL ISSUES
2. PERSONNEL SELECTION AND TRAINING
3. VALIDATION
4. SUPPLIER QUALIFICATION
5. PROCESS CONTROL
6. DOCUMENTATION
7. LABEL CONTROL
8. INCIDENT - ERROR REVIEW
9. INTERNAL ASSESSMENT
10. PROCESS IMPROVEMENT

ANNEX II



Report on the United States Food and Drug Administration Inspections

BY MARTIN BRUCE

RESPONSE TO QUESTIONS POSED BY COMMISSION COUNSEL**1. CONTEXT OF THIS RESPONSE**

As requested I have reviewed the citations made at the recent FDA inspections of Canadian Red Cross Blood Centres. I must stress that all of my comments should be kept in clear context. More specifically, it is not possible to draw absolute conclusions on these citations other than through the eyes of the investigator who was conducting the inspection. Furthermore, in many instances there is too little factual information, both in the citation and in the CRC response, to draw much more than a tentative conclusion. Also, I have already indicated in the report for our Saint John inspection that it is not possible to compare directly the findings of one audit with another. The description of an audit providing a "snap-shot in time" is absolute!

Our inspections and subsequent reports indicated the perceived severity and seriousness of the deficiencies cited and the extent to which they impacted on the safety of the blood system. The FDA inspection reports have not addressed these matters. This further compounds the difficulties in attempting to undertake a retrospective assessment of the FDA reports.

Another important distinction is that the international team had a clear and fairly broad remit to review, as far as was possible, the security of the entire system. We have no understanding of the scope and objectives of the FDA inspections. At face value and from the citations listed, some inspections seem to have been fairly general, one was very detailed. Others appear of very limited scope (eg in Saint John the citations suggested that the focus was exclusively directed towards the computer system (BLIS)), some seem to lack depth.

The international team inspected the systems viewed against an all-embracing, generic concept. The citations listed by FDA inspectors imply that they were inspecting against a series of US regulations. The citations raised in the latter inspections give no insight as to the intended scope or objectives.

Also, I think it is important to indicate that my response is personal and based on:

- the information available to me
- my direct experience and understanding of GMP and the UK (and especially Scottish) Blood Transfusion system
- a good understanding of what is happening elsewhere
- my experience in the 3 CRC inspections
- my personal opinions

Within this context, I have tried to make helpful and objective comments - I hope I

have succeeded.

2. PART 1

2.1 CATEGORISATION OF MATTERS OF CONCERN

The categorisation of deficiencies raised by our inspection process was not intended to be analogous to those of the UK Medicines Control Agency (MCA). This was a conscious decision, taken for a variety of reasons and related specifically to the "critical" MCA category. Some expansion, I'm sure, will be helpful.

A "critical" deficiency is defined by the UK MCA as *"a deficiency considered to represent a source of imminent danger, likely to cause damage to a patient."*

1. As will be noted from the MCA definition, concluding that a deficiency is "critical" is judgemental, subjective and necessitates consideration of a number of complex and interrelated factors.
2. To raise a critical deficiency in a Blood Centre, in some respects, requires exceptionally careful consideration. Pharmaceutical companies can close down until corrective action is taken - the blood supply system is an entirely different proposition. However, it should be understood that if warranted such a citation would be issued. Ensuring the safety of the blood supply system is paramount!
3. To raise a critical deficiency requires the authority to demand urgent corrective action and the ability to re-inspect as appropriate to ensure this has been implemented and is effective.
4. During our inspections we could have found a critical deficiency and still concluded the core elements of the system were safe (indeed, we may have done so - eg at the Saint John inspection we found serious corrosion with some plasma expressors that could have caused pinhole punctures in blood packs. Once identified by the auditors, this deficiency was corrected immediately).
5. Our remit was not to undertake a "regulatory" inspection.

Therefore, "principal matters of concern" were used by the international team to delineate those deficiencies which we judged had greater potential to cause harm. Some of these principal matters perhaps would have been cited as critical but this categorisation would not have influenced our conclusions. **ie if we had felt the core systems of any Centre were unsafe, we would have said so.** The FDA citations were not categorised in this way.

2.2 REVIEW OF FDA CITATIONS

2.2.1 Prioritisation

I have reviewed the FDA citations within the context outlined.

Appendix 1 is a "chronological" summary of the citations that indicates where the same citation was repeated at different inspections and includes my assessment of their significance as individual deficiencies. Their perceived impact on the overall safety of the system is addressed in 2.2.3 and 2.2.5. (It will be clear from appendix 1 that this extends beyond the approach to categorisation used in our reports ie 2 more categories have been added). These tables also include a reference for each citation in a more complete form than is attached as appendix 2.

In Appendix 2, the citations are split into functional areas eg Policy, Donor Selection/Blood Collection etc. Each citation has been placed into a functional area and is dealt with in turn - this is the basis for the Appendix 2 Ref # listed in the tables in Appendix 1 and provides a useful crossreference system.

Each citation is listed in full; if cited at more than one inspection, this is shown and if different wording is used this also is given. The CRC response/s are listed and finally I have commented on the citation within the stated context.

2.2.2 Do the Citations raise additional areas of concern that were not addressed in your inspections?

At the risk of becoming repetitive, it would be normal for inspections to record different non-conformances or "areas of concern". **However, the FDA citations included only three "suggested" principal matters of concern that we did not address. These were almost certainly system-wide problems, two of which indicate a difference in CRC and US FDA policy.**

These latter two citations (appendix 2, #4.2 and #4.5) were the subject of a telephone inquiry I had from Dr Kennedy in Ottawa before my visit. Since I knew these were FDA citations and were receiving attention by CRC I felt it unnecessary to raise them. You will note that the area covered in appendix 2 #4.2 is included within the "international checklist". (Appendix 3 to the Centre audit reports.)

Appendix 2 #2.7 is the only other "principal matter of concern" that we did not raise.

This raises problems that might arise from not having a nationally linked donor data base and donor referral request.

2.2.3 Do the FDA citations affect in any way the "system wide" conclusions that you have drawn? If so, why and how?

Again, within context, I would conclude no!

2.2.4 *Do the FDA citations support any conclusions about the overall process (CRC); or do they reflect isolated deficiencies?*

I would suggest the FDA citations confirm the international inspection team view that the lack of an effective integrated computer system, and documented deficiencies with the existing system, give serious cause for concern.

Also, there is abundant confirmation that GMP systems and comprehension are at an early stage of development. Our concerns about the autocratic style and problems caused by National Office are supported by many specific FDA citations and by the general approach taken by CRC in responding to FDA citations.

Beyond these specifics and the conclusion that the core elements of the system are secure, the citations cannot be used to support conclusions about the overall CRC process. As mentioned in the "context" section, we do not know the scope and objectives of the FDA inspections and the citations listed imply that the scope differed from site to site. **However, it is relevant that most of the important problems cited appeared to be "system" problems that probably would have been found in all CRC Centres.**

2.2.5 *Evaluate the FDA citations from the perspective of overall safety. Why do you come to this conclusion?*

Audits are an essential element of GMP and, even in well developed GMP systems, it would be normal to find non-compliances - that's why audit is done!

Having viewed numerous UK (MCA) regulatory inspection reports, I would suggest that in the UK, Blood Transfusion Centres who received reports similar to those issued by the FDA to CRC Blood Centres would not have their licence withdrawn, nor would they be prevented from operating. Rather, they would be expected to develop and implement a programme of corrective action within a timeframe that reflected the seriousness of the problem. **This reflects my view that the FDA citations, in the stated context, do not indicate that the CRC blood supply is unsafe.**

As mentioned, the FDA citations confirm some of this international audit team findings but do not change the overall conclusions of our report.

Finally, of a total of 88 "different" FDA citations, 4 were assessed as "principal matters of concern". Only 6 of the FDA inspections produced such citations (3 in Toronto, 1 in Halifax; 1 in Edmonton, Winnipeg and Hamilton (these were a "repeat" from Toronto); 1 in Vancouver (another "repeat" from Toronto)).

As a corollary, the "international" team cited a total of 34 different principal and major matters of concern. 3 of these were cited by the FDA investigators. (Lack of

expiry date on blood components; multiple problems with the BLIS computer system and, possibly, failure to note that >1% of Health Assessment Questionnaires are not completely documented). **It is worth emphasising that in spite of raising these 34 different "principal and other major matters of concern", the international inspection team concluded that the core elements of the CRC blood supply were secure.**

2.2.6 CRC Response to FDA citations

The CRC have responded very quickly to the FDA citations but it seems that no attempt has been made to prioritise and plan implementation of corrective action. It is not clear whether the suggested implementation timeframe is realistic for National or the Centres. Certainly, our inspections suggest that the timeframe for Centres is not.

P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)	No of Citations (repeats)	DESCRIPTION OF FDA CITATION	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (5)	8 (4)	13 (8)	Appendix 2 Ref #	MB "ASSESSMENT"
<p> P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance) </p> <p><i>Madam</i></p>	Inspection W = worded differently	DESCRIPTION OF FDA CITATION														
		Autologous blood products are shipped to the US without a US licence for the product.	#1												1.1	D
		Source plasma is shipped to the US without a US licence for the product.	#2												1.2	D
		Blood products are labelled with the collection date and no expiration date.	#3						W #4	W #3	W #19				5.1	P
		Blood products are not tested for the Hepatitis B core antigen (anti-HBc).	#4						W #3	W #1					4.1	U
		Blood group labels are applied to blood products prior to testing based on prior test results. This has resulted in 25-30 mislabelled units per month. There is no written record into the discrepancies including conclusions and follow up.	#5								W #20				2.1	U
		There are no procedures for quarantine and retrieval of in-date units from prior collections for donors having repeatedly reactive screening tests for antibodies to HIV.	#6										W #6		4.2	P
		Donor screening procedures for whole blood donors do not require determination of donor temperature or blood pressure nor, examination of both arms for punctures or scars indicative of self injected narcotics.	#7		W #1a,c		W #1a,c	W #1a,c	W #2	W #6	W #22	W #8		W #10	2.2	D
		Donor screening procedures for source plasma do not include: an annual physical by a physician; the donor weight is not taken; an examination of donor arms for punctures or scars indicative of self-injected narcotics; and donors are not withdrawn from the program until acceptable serum protein results are received.	#8		W #1b,c,d		W #1b,c	W #1b,c	W #1	W #2	W #23				2.3	O

[illegible]

<p><i>March 1999</i></p> <p>P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)</p>	No of Citations (repeat)	DESCRIPTION OF FDA CITATION	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (5)	8 (4)	13 (8)	Appendix 2 Ref #	MB "ASSESSMENT"
	Inspection W = worried differently		TORONTO 18-22 JULY MARY CARDEN	HALIFAX 12-14 SEPT MARY CARDEN	SUDBURY 12-14 SEPT SANDRA WHITE	SAINT JOHN NB 15-16 SEPT MARY CARDEN	WINDSOR 19 SEPT SANDRA WHITE	LONDON 19-21 SEPT SANDRA WHITE	EDMONTON 19-21 SEPT RONNIE E JACKSON	WINNIPEG 19-22 SEPT ALICE KRIVITSY	HAMILTON 19-22 SEPT ERIN HYER	SASKATOON 26-27 SEPT LISA ALTHAR	VANCOUVER 26-30 SEPT STEPHANIE KERSTEN	REGINA 29-30 SEPT LISA ALTHAR		
			#17	#3		#1					#18	#2	#8	#3	2.6	O
			#19											#4	3.2	O
				#1							#2	#1		#1	4.6	D
				#3											4.7	U
				#4											4.8	U
				#5											4.9	M
				#6											4.10	M/O

* Please see initial remarks - computing problems as a general issue, were a principal matter of concern of the international team

No of Citations (repeats)		Appendix 2 Ref #	MB "ASSESSMENT"
Inspection W = worked differently			
P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)			
19 TORONTO 18-22 JULY MARY CARDEN			
11 HALIFAX 12-14 SEPT MARY CARDEN			
5 SUDBURY 12-14 SEPT SANDRA WHITE			
10 SAINT JOHN NB 15-16 SEPT MARY CARDEN			
3 WINDSOR 19 SEPT SANDRA WHITE			
4 LONDON 19-21 SEPT SANDRA WHITE			
10 EDMONTON 19-21 SEPT RONNIE E JACKSON			
9 WINNIPEG 19-22 SEPT ALICE KRIVITSKY			
38 HAMILTON 19-22 SEPT ERIN HYER			
9 SASKATOON 26-27 SEPT LISA ALTHAR			
8 VANCOUVER 26-30 SEPT STEPHANY KERSTEN			
13 REGINA 29-30 SEPT LISA ALTHAR			
		2.7	P*

DESCRIPTION OF NON COMPLIANCE		Appendix 2 Ref #	P*
Individuals are allowed to donate under different donor numbers, which could result in the inability to trace blood products to the appropriate donor and could result in the donor not being identified as deferred when appropriate.			
User documentation for computer services is inadequate.		3.3	U
Written procedures document "QA-610 Calibration of Shaker" and quality control records fail to identify/indicate the known standardised weight and/or acceptable limit which ensures blood containers (collection bags) are filled with the proper amount of donor-collected blood		2.8	O
Blood collection bags are not labelled with proper donor identification information (as the pilot tubes are) prior to blood collection from the donor. An example of this was observed on 9/13/94 during the preparation of an apheresis male donor, donor collection unit FA 216873-9.		2.9	O
Stacked plastic trays containing ABO/BND+ blood products which were stored in the laboratory walk-in refrigerator and available for release/distribution, lacked conspicuous identification by blood type (Positive Rh).		5.3	O
Blood/blood products are not visually inspected daily or periodic basis i.e. during daily inventory checks, and the activity is not indicated or addressed in written procedures		5.4	D
Training records for the BLS System are not adequate: a) there are no written procedures for training b) there are no written procedures for training updates c) there are no procedures in place for assessing the training performed and the adequacy of it		3.4	O

DESCRIPTION OF NON COMPLIANCE

Individuals are allowed to donate under different donor numbers, which could result in the inability to trace blood products to the appropriate donor and could result in the donor not being identified as deferred when appropriate.

User documentation for computer services is inadequate.

Written procedures document "QA-610 Calibration of Shaker" and quality control records fail to identify/indicate the known standardised weight and/or acceptable limit which ensures blood containers (collection bags) are filled with the proper amount of donor collected blood

Blood collection bags are not labelled with proper donor identification information (as the pilot tubes are) prior to blood collection from the donor. An example of this was observed on 9/13/94 during the preparation of an apheresis male donor, donor collection unit #A 216873-9.

Stacked plastic trays containing ABO/RhD + blood products which were stored in the laboratory walk-in refrigerator and available for release/distribution, lacked conspicuous identification by blood type (Positive Rh).

Blood/blood products are not visually inspected daily or periodic basis i.e. during daily inventory checks, and the activity is not indicated or addressed in written procedures

Training records for the BLIS System are not adequate:

- a) there are no written procedures for training
- b) there are no written procedures for training updates
- c) there are no procedures in place for assessing the training performed and the adequacy of it

not please read 2.7.3

- but see 3.5.3

[illegible]

but see 3.11/3.5.3

No of Citations (repeats)	DESCRIPTION OF FDA CITATION	No of Citations (repeats)	Inspection W = worked differently	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (5)	8 (4)	13 (8)	Appendix 2 Ref #	MB "ASSESSMENT"
	<p><i>Major Concern</i></p> <p>P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)</p>			TORONTO 18-22 JULY MARY CARDEN	HALIFAX 12-14 SEPT MARY CARDEN	SUBBURY 12-14 SEPT SANDRA WHITE	SAINT JOHN NB 15-16 SEPT MARY CARDEN	WINDSOR 19 SEPT SANDRA WHITE	LONDON 19-21 SEPT SANDRA WHITE	EDMONTON 19-21 SEPT RONNIE E JACKSON	WINNIPEG 19-22 SEPT ALICE KRIVITSKY	HAMILTON 19-22 SEPT ERIN HYER	SASKATOON 26-27 SEPT LISA ALTHAR	VANCOUVER 26-30 SEPT STEPHANY KERSTEN	REGINA 29-30 SEPT LISA ALTHAR		
	DESCRIPTION OF FDA CITATION									#8						7.5	O
	Glycine soya reagent (QC control check for insuring proper enzyme treatment of reagent red blood cells) fails to bear an appropriate expiration date.									#10						7.6	U
	Validation protocols covering installation and field check-out procedures of blood cell processing and storage equipment are not dated, and fail to show that they have been reviewed and/or approved prior to implementation.										#4					2.12	U
	Procedure QA 67 "Autologous Bivox Transfusion" conflicts with "Donor Selection Criteria Manual - Autologous" as they do not have the same requirements in each document.										#5					1.3	U
	The hemaglobin requirement for subsequent units of blood collected from Autologous Donors is below the recommended FDA criteria for hemaglobin/hematocrit.																
	The arm scrub used on the donor prior to the venipuncture is not done for 30 seconds.										#7					2.13	O
	Only a 70 day previous donation inventory retrieval is done for units from donors testing repeatedly reactive for HBsAg.											#3				4.11	O
	No validation of the computer system BLIS software and hardware is done by site computer personnel, including when new procedures are implemented.											#4				3.12	O
	This site uses an automated "sort" software programme for final product labelling and release for use. There are no written training procedures for "sort" and employees are not trained with test data, but rather "on-line".											#7				3.13	M*

* but see 3.5.3A.11/3.13.3

<p><i>Martin Buer</i></p> <p>P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)</p>	No of Citations (repeats)	<p>Inspection</p> <p>W = worked differently</p>	DESCRIPTION OF FDA CITATION	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (5)	8 (4)	13 (8)	Appendix 2 Ref #	MB "ASSESSMENT"
			TORONTO 18-22 JULY MARY CARDEN		HALIFAX 12-14 SEPT MARY CARDEN	SUDBURY 12-14 SEPT SANDRA WHITE	SAINT JOHN NB 15-16 SEPT MARY CARDEN	WINDSOR 19 SEPT SANDRA WHITE	LONDON 19-21 SEPT SANDRA WHITE	EDMONTON 19-21 SEPT RONNIE E JACKSON	WINNIPEG 19-22 SEPT ALICE KRAVITSY	HAMILTON 19-22 SEPT ERIN HYER	SASKATOON 26-27 SEPT LISA ALTHAR	VANGOUVER 26-30 SEPT STEPHANY KERSTEN	REGINA 29-30 SEPT LISA ALTHAR		
												#8	W			3.14	O
												#9	#3			3.15	O
												#6				2.14	O
												#11				3.16	O
												#12				2.15	O
												#13				5.7	O*
												#14				5.8	M≠
												#15				7.7	O

* Based on what I have noted elsewhere, not on what was cited

≠ Please see 5.8.3

<p><i>Martin Bruce</i></p> <p>P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)</p>	No of Citations (repeats)	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (6)	8 (4)	13 (8)	Appendix 2 Ref #	MB - ASSESSMENT											
	Inspection W = wounded differently	TORONTO 18-22 JULY	MARY CARDEN	HALIFAX 12-14 SEPT	MARY CARDEN	SUDBURY 12-14 SEPT	SANDRA WHITE	SAINT JOHN NB 15-16 SEPT	MARY CARDEN	WINDSOR 19 SEPT	SANDRA WHITE	LONDON 19-21 SEPT	EDMONTON 19-21 SEPT			RONNIE E JACKSON	WINNIPEG 19-22 SEPT	ALICE KRIVITSY	HAMILTON 19-22 SEPT	ERIN HYER	SASKATOON 26-27 SEPT	LISA ALTHAR	VANCOUVER 26-30 SEPT	STEPHANY KERSTEN	REGINA 29-30 SEPT	LISA ALTHAR
	DESCRIPTION OF NON COMPLIANCE																									
	The SOP describing instructions for blood group determination done prior to donation does not specify how to make the determination for type "AB", nor gives adequate instructions on how to perform the rudimentary test.																									
	Review of 20 plasmapheresis donor records revealed that 4 records do not contain a photo ID of the donor as required.																									
	This site is using quad whole blood units which are already prelabelled as "Rh pos". Current procedure is to apply a "Rh neg" or "Rh pos" sticker over the label.																									
	Component labels are placed on the satellite bags prior to the completion of component preparation.																									
	There is no written procedure describing component preparation for cryoprecipitant product which can be shipped as plasma for further manufacturing use.																									
	The current short supply agreement, dated January 1992, discuss fractionation of products defined as Recovered Plasma, apheresis plasma and stored plasma. The CRC prepares and ships to Miles Inc for fractionation. "Recovered Plasma Frozen less than 15 hours (RP-15)", and "Recovered Plasma CRP" which may contain a product labelled as plasma and "cryoprecipitant".																									
Review of lookback files (52-94-004) revealed that for donation date 1/26/94, it was noted there may be "...possible carryover on Hamilton AT". The site investigation of this incident is not contained within this file.																										
The results of the investigation done by National for the possibility of carryover for the Hamilton AT were not transmitted to this site until 9/21/94.																										

<p><i>Martin</i></p> <p>P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)</p>	No of Citations (repeats)	<p>Inspection</p> <p>W = worded differently</p>	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (5)	8 (4)	13 (8)	Appendix 2 Ref #	MB - ASSESSMENT
	DESCRIPTION OF FDA CITATION															
			TORONTO 18-22 JULY MARY CARDEN	HALIFAX 12-14 SEPT MARY CARDEN	SUBBURY 12-14 SEPT SANDRA WHITE	SAINT JOHN NB 15-16 SEPT MARY CARDEN	WINDSOR 19 SEPT SANDRA WHITE	LONDON 19-21 SEPT SANDRA WHITE	EDMONTON 19-21 SEPT RONNIE E JACKSON	WINNIPEG 19-22 SEPT ALICE KRIVITSY	HAMILTON 19-22 SEPT ERIN HYER	SASKATOON 26-27 SEPT LISA ALTHAR	VANCOUVER 26-30 SEPT STEPHANY KERSTEN	REGINA 29-30 SEPT LISA ALTHAR	4.14	0
											#33				4.15	0
											#36				4.16	0
											#37				6.2	0
											#38				4.17	0
											#39				8.1	0

No of Citations (repeats)		DESCRIPTION OF FDA CITATION	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (5)	8 (4)	13 (8)	Appendix 2 Ref #	MB "ASSESSMENT"
Inspection W = Wounded differently																
Noting Bruce P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)		DESCRIPTION OF FDA CITATION	TORONTO 18-22 JULY	HALIFAX 12-14 SEPT	SUBBURY 12-14 SEPT	SAINT JOHN NB 15-16 SEPT	WINDSOR 19 SEPT	LONDON 19-21 SEPT	EDMONTON 19-21 SEPT	WINNIPEG 19-22 SEPT	HAMILTON 19-22 SEPT	SASKATOON 26-27 SEPT	VANCOUVER 26-30 SEPT	REGINA 29-30 SEPT		
		There is no documentation of training for the Laboratory Manager or Computer Services Supervisor to show they have received specific training in the operations they supervise.													6.3	0
		The approved written procedure for calibration of the Sorvall RC-3B centrifuges used for the preparation of recovered plasma does not include acceptable ranges or method of corrective actions that should be conducted for results that are out of range.													5.12	0
		There is no written procedure for calibrating the scales used in the preparation of recovered plasma.													5.13	0
		Arm preparation procedures do not include a method and duration of scrub technique, but only an application of Povidone-Iodine in an outward, circular pattern.													2.18	0
		Of approximately 250 Health Assessment Questionnaires reviewed 3 did not contain complete documentation of donor suitability.													2.19	M/O
		Personnel performing weekly volume verification of the Ortho Summit and personnel reviewing the Ortho Summit volume verification report dated 9/20/94 (for serial number 1033 048) did not note values deviated from Manufacturers Specifications.													4.18	0
		Personnel performing weekly volume verification of the Ortho Summit 8/25/94 to the present failed to enter the calibrated value of the manual pipette utilized to perform volume verification. The manual pipette was calibrated to deliver a volume of 99.89 on 8/25/94. Volume verification reports dated after 8/25/94 indicate a value of 101.5 was used to perform weekly volume verification.													4.19	0

No of Citations (repeats)		Inspection W = worded differently	19	11 (4)	5 (1)	10 (2)	3 (2)	4 (1)	10 (5)	9 (6)	38 (13)	9 (5)	8 (4)	13 (8)	Appendix 2 Ref #	MB "ASSESSMENT"
<div><i>Noting</i></div> <div>P = Principal Matter of Concern M = Other Major Matter of Concern O = Other Matter of Concern D = of Doubtful or no relevance to safety in the Canadian Red Cross BTS U = Unable to assess (but suspect of minor importance)</div>			DESCRIPTION OF FDA CITATION													
			The manufacturer's operator's manual for the Ortho Summit requires the use of a direct-displacement pipette for weekly volume verification. It has not been determined that the Gilson Pipetman in use for weekly volume verification of the Ortho Summit is a direct-displacement pipette.													
			There are no written procedures for calibration of the Diatec Testing Laboratory incubator thermometers													
			Written procedures (COP EQ 207) require temperature readings of the glass and digital thermometers, differing by greater than 2°C to be repeated within 60 minutes; however, there is no documentation of the actual time readings are taken to ensure this is performed as required													
			An out of range temperature of between -16°C and -17°C observed for freezer #1 temperature recording chart dated 4/12/1994 was not explained as required in COP EQ 207.													
			Procedures used in Centrica are not always signed and dated as approved per procedure CQ 1000. Procedures observed include Registrar Training and Incident reporting.													
			There are no written procedures for documenting lot numbers and expiry dates of Providence iodine swabs used for arm preparation prior to venepuncture.													

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1. "POLICY" CITATIONS

1.1.1 FDA CITATION

Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#1. *Autologous blood products are shipped to the US without a US license for the product*

1.1.2 CRC RESPONSE

"Shipment of autologous units into the United States has been stopped. Since January 1994, a total of 15 units (five different patients) collected according to Canadian requirements were shipped under our registration number 9611971 (attached)".

1.1.3 MB COMMENT

This citation is not a safety issue but illustrates what is, perhaps, a "constitutional" matter that needs to be addressed.

1.2.1 FDA CITATION

Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#2. *Source plasma is shipped to the US without a US license for the product*

1.2.2 CRC RESPONSE

"Following our telephone conversation on 5 August 1994 with Ms Mary Gustafson, Division of Blood Applications, CBER, all shipments of source plasma were stopped. A letter was faxed to Dr K Zoon, Director, CBER, on 18 August 1994 indicating that source plasma will not be shipped to the United States until the Centres collecting source plasma have a US FDA licence".

1.2.3 MB COMMENT

It seems likely that in the US, this requirement has been introduced because the majority of source plasma donors in the US are paid and therefore, as is internationally recognised, represent a higher risk category of donors. All Canadian source plasma donors are non-remunerated volunteers and therefore such plasma represents a safer starting material for fractionated products.

The process and motive for changing a policy whereby it was deemed significant for CRC merely to be FDA registered, to one where a product licence was required for export of source plasma to the US needs to be very carefully established.

The sense of such a decision, and its timing, is even less clear against an understanding that plasma from CRC is fractionated discretely by Miles who apparently undertake strip down/systems clearance before and after fractionating CRC plasma. (Although the validity of this claim perhaps should be assessed at an independent audit of Miles!) Also, all fractionated products that are generated from

CRC plasma are believed to be returned to CRC.

This is not a safety issue.

1.3.1 FDA CITATION

Toronto 18-22 July 1994. Ms Mary Carden (19 Citations)

- #5. *The hemoglobin requirement for subsequent units of blood collected from Autologous Donors is below the recommended FDA criteria for hemoglobin/hematocrit*

1.3.2 CRC RESPONSE

"A National SOP addressing this subject will be developed and implemented before applying for licensure for the shipment of autologous blood to the US".

1.3.3 MB COMMENT

I have insufficient detail to comment, but the matter probably is a minor concern.

1.4.1 FDA CITATION

Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

- #30. *The current short supply agreement, dated January 1992, discusses the fractionation of products defined as Recovered Plasma, apheresis plasma, and stored plasma. The CRC prepares and ships to Miles, Inc. for fractionation "Recovered Plasma Frozen Less than 15 Hours (RP-15)", and "Recovered Plasma (RP)", which may contain a product labelled as plasma and "cryosupernatant"*

1.4.2 CRC RESPONSE

"The short supply agreement and product labelling practices will be harmonised. This is scheduled to be discussed at a meeting with the FDA to be arranged soon".

1.4.3 MB COMMENTS

Not an important safety issue.

2. "DONOR SELECTION/BLOOD COLLECTION" CITATIONS

2.1.1 FDA CITATION

ABO group labels are attached at collection before the "test of record" is performed.

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#5. *Blood group labels are applied to products prior to testing based on prior test results. This has resulted in 25-30 mislabelled units per month. There is no written record into the discrepancies including conclusions and follow-up*

ii. Hamilton 19 -22 Sept 1994. Ms Erin Hyer (38 Citations)

#20. *Blood group labels (ABO) are applied to blood products using a rudimentary test done in nursing, prior to completion of testing, and based on previous results*

2.1.2 CRC RESPONSE

i. Response to Toronto Citation

"This observation was identified from the review of the centres error/incident records which form part of our investigation and corrective action procedure. A system is in place to correct errors (please see attached SOP "Processing of Wrong Groups"). Of the 25-30 units mislabelled at registration, none were released for transfusion with an incorrect label".

ii. Response to Hamilton Citation

"In Canada blood group typing is done at the clinic to facilitate processing of whole blood units in the clinic prior to submission to the laboratory. The test of record is done in the laboratory and supersedes the testing at the clinic. Any discrepancy is corrected and documented in the laboratory".

2.1.3 MB COMMENTS

This is a major matter of concern identified in each of our inspection reports. Whilst we found no evidence that incorrectly labelled donations left the Centres, the procedures needed to correct these errors were very complex and time consuming.

2.2.1 FDA CITATION

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#7. *Donor screening procedures for whole blood do not include a determination of the donor temperature and blood pressure or require*

an examination of donor arms for punctures or scars indicative of addiction to self-injected narcotics

ii. Sudbury 12-14 Sept 1994. Ms Sandra White (5 Citations)

#1. *In the review of volunteer donor records and donor operation procedures:*

- a. *donor screening fails to include and document donor temperature, pulse, blood pressure, weight checks, and inspection of arms for needle puncture/scars*
- c. *the above described screening checks are not included as part of the applicable written donor procedures*

iii. Edmonton 19-21 Sept 1994. Mr Ronnie E Jackson (10 Citations)

#2. *Prior to 3/1/94, vital signs (temperature, blood pressure and pulse) of whole blood donors were not taken or recorded prior to donation*

iv. Winnipeg 19-22 Sept 1994. Ms Alice Krivitsy (9 Citations)

#6. *Allogeneic donors are not evaluated for blood pressure, pulse and temperature prior to donating*

v. Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

#22. *Donor screening procedures for whole blood do not include a determination of the donor's temperature and blood pressure*

vi. Saskatoon (#8) 26-27 Sept 1994. Ms Lisa Althar (9 Citations)

and

vii. Regina (#10) 29-30 Sept 1994. Ms Lisa Althar (13 Citations)

Procedures for the collection of whole blood do not require donor temperature and blood pressure determinations, and HIV risk factors are not verbally presented to donors

2.2.2 CRC RESPONSE

i. Response to Toronto Citation

"Canadian regulations for whole blood donors do not require determination of donor temperature or blood pressure nor, examination of both arms for punctures or scars indicative of self-injected narcotics. This will be implemented prior to application for a US licence".

ii. **Response to Sudbury Citation**

"Documentation of donor temperature, pulse, blood pressure and weight are not required for whole blood donors according to Canadian regulations. We understand that weight checks are not required for whole blood donors. Additional SOPs have been piloted in three Centres to cover this area. They will be implemented in the remaining Centres before applying for licensure. A National directive has just been issued to implement a documented check of both arms for scars or needle tracks".

iii. **Response to Edmonton Citation**

"As indicated, this observation recognizes that Edmonton Centre is now in compliance with US standards".

iv. **Response to Winnipeg and Hamilton Citation**

"Documentation of donor blood pressure, pulse and temperature are not required for whole blood donors according to Canadian regulations. National SOPs addressing this issue have been piloted and will be implemented in all Centres before applying for licensure".

v. **Response to Saskatoon Citation**

"SOPs which meet FDA guidelines have been developed and will be implemented before applying for licensure".

vi. **Response to Regina Citation**

"Documentation of donor blood pressure, pulse and temperature are not required for whole blood donors according to Canadian Regulations. National SOPs addressing the requirements for donor temperature, blood pressure and verbally presenting HIV risk factors to donors have been developed and will be implemented prior to application for licensure".

2.2.3 **MB COMMENTS**

The soundings I have taken from UK experts indicate that temperature and pulse are considered of no proven value in the donor assessment process and certainly are not safety matters. It is that inspection of both arms for evidence of narcotics abuse is of limited value, perhaps only where suspicions are aroused. FDA policy on this matter may be more appropriate in US. Also, the value of arm inspection is further diminished by the appreciation that drug users use veins other than in their arms.

2.3.1 FDA CITATION

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

- #8. *Donor screening procedures for Source Plasma do not include: an annual physical by a physician; the donor weight is not taken; an examination of donor arms for punctures or scars indicative of addiction to self-injected narcotics, and donors are not withdrawn from the program until acceptable serum protein results are received*

ii. Sudbury 12-14 Sept 1994. Ms Sandra White (5 Citations)

- #1. *In review of donor records and donor operating procedures:*
- b. *inspection of arms for needle puncture/scars of apheresis donors is not performed and/or documented*
 - d. *plasmapheresis donor records re: donors Y01504724-3, Y92061835-2 and Y92002341-8 revealed that these donors had not received annual physical examinations since their initial screening/donation, which occurred between 1988 and 1991. Additionally, written apheresis procedures lack this requirement.*

iii. Windsor 19 Sept 1994. Ms Sandra White (3 Citations)

and

iv. London 19-21 Sept 1994. Ms Sandra White (4 Citations)

- #1. *In review of volunteer donor records and operating procedures, prior to 8/94 (Windsor) and 7/94 (London)*
- a. *donor screening failed to include/document donor temperature, pulse, blood pressure, donor weight, and arm inspections for needle scars/punctures*
 - b. *arm inspection of apheresis donors were not performed or documented; and*
 - c. *these screening checks were not included as part of applicable written donor procedures*

v. Edmonton 19-21 Sept 1994. Mr Ronnie E Jackson (10 Citations)

- #1. *Current donor screening procedures for Source Plasma do not include criteria requiring annual examinations by centre physicians*

vi. **Winnipeg 19-22 Sept 1994. Ms Alice Krivitsy (9 Citations)**

- #2. *A physical examination is not given to plasmapheresis donors at the time of the first donation and annually thereafter*

vii. **Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)**

- #23. *Donor screening procedures for plasma do not include an annual physical by the on site physician*

2.3.2 **CRC RESPONSE**

i. **Response to Toronto and Edmonton Citations**

"This procedure will be formalized to comply with FDA requirements and all procedures will be implemented prior to our application for a US licence".

ii. **Response to Sudbury, Winnipeg and Hamilton Citations**

"SOPs which meet FDA guidelines have been developed and will be implemented before applying for licensure".

iii. **Response to Windsor and London Citations**

- a. *"For apheresis donors, temperature, pulse, blood pressure, and donor weight are documented according to procedures. For whole blood donors, the screening for temperature and blood pressure was started in July 1994. We understand that weight checks are not required for whole blood donors.*
- b. *Arm inspections for all donors, whole blood and apheresis, were started recently.*

As indicated in the observation these procedures were implemented prior to the inspection".

2.3.3 **MB COMMENTS**

These citations are not major safety issues and were dealt with more than adequately by Dr Hearst at the Hearing, see also my comments on previous citation (ie 2.2.3).

It is noted that the citations at 2.3.2iii and iv appear erroneous (ie procedures were in place but it is not known if they were documented).

2.4.1 FDA CITATION

- i. **Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)**
 - #9. *AIDS educational information is not provided to donors at each donation. Questions concerning risk behaviour for HIV infection are not verbally presented to donors*
- ii. **Winnipeg 19-22 Sept 1994. Ms Alice Krivitsy (9 Citations)**
 - #9. *Donors do not acknowledge in writing that they have read and understood the AIDs educational material. The questions are not presented to the donor verbally*
- iii. **Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)**
 - #24. *Questions concerning risk behaviour for HIV infection are not verbally asked of to donors*
- iv. **Saskatoon (#8) 26-27 Sept 1994. Ms Lisa Althar (9 Citations)**

and
- v. **Regina (#10) 29-30 Sept 1994. Ms Lisa Althar (13 Citations)**

(Included within another citation)

HIV risk factors are not verbally presented to donors
- vi. **Vancouver 26-30 Sept 1994. Ms Stephany Kersten (8 Citations)**
 - #1. *Questions concerning high risk behaviour (for AIDS) are not verbally presented to whole blood donors at the time of each donation*
 - #7. *Standard Operating Procedures do not require the phyisican performing the initial and annual physical for plasmapheresis donors to:*
 - a. *verbally present the full text of the AIDS educational information to the donor*
 - b. *verbally question the donor concerning high risk behaviour*

2.4.2 CRC RESPONSE

- i. **Response to Toronto Citation**

"Our Donor Health Questionnaire, completed by the donor at each donation,

does provide the information required by FDA Memorandum of April 1992. Risk behaviour for HIV infection will be verbally presented to all donors prior to our application for an FDA licence".

ii. Response to Citations at Winnipeg, Hamilton, Saskatoon, Regina and Vancouver

"SOPs which meet FDA guidelines have been developed and will be implemented before applying for licensure".

2.4.3 MB COMMENTS

The first part of the Toronto Citation seems to have been erroneous (as confirmed in the CRC response and Dr Heart's testimony). The second point possibly is of some value but probably is not a major safety issue and, again, was well covered by Dr Hearst. It is, however an FDA requirement.

2.5.1 FDA CITATION

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#10. There are no procedures for QC of copper sulfate used to determine donor hemoglobin

ii. Windsor 19 Sept 1994. Ms Sandra White (3 Citations)

#2. Up until 9/94, there was no written procedure or records documenting the testing of each copper sulfate lot received prior to use

iii. Winnipeg 19-22 Sept 1994. Ms Alice Krivitsy (9 Citations)

#8. Copper sulfate, used to determine if the donor's hemoglobin level is acceptable, is not quality controlled on a daily basis

iv. Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

#25. Quality control for the Copper Sulfate solutions, used in the determination of hemoglobin for donor acceptability, is not performed

2.5.2 CRC RESPONSE

i. Response to Toronto Citation

"This procedure will be written and implemented or, an alternative method introduced for the determination of donor hemoglobin prior to our application for a US licence".

ii. Response to Windsor Citation

"As indicated in the observation this Quality Control procedure was implemented prior to the inspection".

iii. Response to Winnipeg Citation

"SOPs have been developed for the quality control of copper sulfate and this includes the requirement for quality control to be performed on a daily basis. This will be implemented Nationally by the end of October 1994".

iv. Response to Hamilton Citation

"A National procedure for Quality Control of Copper Sulfate will be in place by 30 September 1994".

2.5.3 MB COMMENTS

This is not an important safety issue but is a minor GMP deficiency. Several other minor points:

- . Copper Sulphate deteriorates on exposure to light, therefore stocks need to be in dark bottles, away from light. This is not an FDA requirement.
- . Daily quality control seems excessive
- . Again an FDA investigation has cited a problem that has already been corrected (in Windsor)
- . National response to Winnipeg citation stated a National SOP would be in place by the end of October 1994. The response re Hamilton stated 30 September 1994. In fact the later date was the date referred to by us in our report on Saint John (see 1.1.7).

2.6.1 FDA CITATION

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

- #17. *All records of donor deferrals, additions and deletions do not include the reason the change was being made***

2.6.2 CRC RESPONSE

"A formal procedure including the reason for changes was implemented as of January 1994. All records since that date include this information".

2.6.3 MB COMMENTS

I think the point being made by Mary Carden has been missed by CRC ie my interpretation is that the system that was implemented as of January 1994 was not being followed. However, it is difficult to comment without all available information. This is a minor problem.

2.7.1 FDA CITATION

Halifax 12-14 Sept 1994. Ms Mary Carden (11 Citations)

- #8. *Individuals are allowed to donate under different donor numbers, which could result in the inability to trace blood products to the appropriate donor and could result in the donor not being identified as deferred when appropriate*

2.7.2 CRC RESPONSE

"Although a duplicate record can be created for a donor from another Centre, each record contains complete demographics to allow tracing of the donated unit.

Procedures will be developed to identify such donors and documentation linkages between duplicate donor numbers to aid in lookback investigations. To prevent release of units from such donors, SOPs will be developed to keep such units in quarantine until their deferral status has been checked with the other Centre. This will be completed before application for licensure".

2.7.3 MB COMMENT

It is difficult to comment without further information. However, if the CRC response is confirming that they did not have procedures in place to ensure that all donations given (in any CRC Centre) can be traced, this is a major problem. eg if "John Smith" tested repeatedly reactive, confirmed positive for anti-HIV in the Toronto Centre and gave a donation 4 months ago in Winnipeg, the earlier donation would not be traced.

SUDBURY

There were two further citations at the Sudbury inspection (12-14 Sept 1994; 5 Citations; Ms Sandra White) that were blood collection issues ie:

2.8.1 FDA CITATION

- #2. *Written procedures document "QA610 Calibration of Shaker", and quality control records fail to identify/indicate the known standardised weight and/or acceptable limit which ensures blood containers (collection bags) are filled with the proper amount of donor-collected blood*

2.8.2 CRC RESPONSE

"Centres will immediately revise the Centre operating procedure to require that the identification number and the actual weight of the Sebra calibration weight are recorded in the shaker calibration records. Staff will be trained and the training documented. These requirements will be added to a new National SOP for this process, which will be implemented nation-wide before applying for FDA licensure".

2.8.3 MB COMMENT

Minor GMP non compliance.

2.9.1 FDA CITATION

#3. Blood collection bags are not labelled with proper donor identification information (as the pilot tubes are) prior to blood collection from the donor. An example of this was observed on 9/13/94 during the preparation of an apheresis male donor, donor collection unit #A216873-9

2.9.2 CRC RESPONSE

"This issue has been addressed in the new SOPs which will be implemented before application for licensure".

2.9.3 MB COMMENT

Minor deficiency.

EDMONTON

There were two further citations at the Edmonton inspection (19-21 Sept 1994; 10 Citations; Mr Ronnie E Jackson) that were blood collection issues, ie:

2.10.1 FDA CITATION

#5. Donormatic blood collection scales are not calibrated each day of use (in the main centre only)

2.10.2 CRC RESPONSE

"As of 21 September 1994, all donormatics in the main centre are being calibrated daily".

2.10.3 MB COMMENT

Minor deficiency.

2.11.1 FDA CITATION

#6. The minimum and maximum weight volume requirements listed in Centre Operating Procedure (COP) - Donormatic Calibration Check and records are

different than the minimum and maximum ranges allowed by the equipment manufacturer

2.11.2 CRC RESPONSE

"The Centre Operating Procedure has now been updated to reflect the change in manufacturer's instructions".

2.11.3 MB COMMENT

Minor deficiency.

WINNIPEG

There were three further citations at the Winnipeg inspection (19-22 Sept 1994; 9 Citations; Ms Alice Krivitsy) that were blood collection issues ie:

2.12.1 FDA CITATION

#4. *Procedure QA67 "Autologous Blood Transfusion" conflicts with "Donor Selection Criteria Manual - Autologous" as they do not have the same requirements in each document*

2.12.2 CRC RESPONSE

"Autologous shipments to the United States have been discontinued as of August 5th, 1994. SOP QA67 will be revised to conform with the Donor Selection Criteria Manual - Autologous, and procedures will be implemented to assure that future revisions to the Donor Selection Criteria Manual will be reflected in the SOP".

2.12.3 MB COMMENTS

Cannot comment on degree of seriousness since I don't know what the contradictions were. Probably a minor deficiency.

2.13.1 FDA CITATION

#7. *The arm scrub used on the donor prior to the venepuncture is not done for 30 seconds*

2.13.2 CRC RESPONSE

"A double arm scrub in accordance with US FDA guidelines is in the process of being implemented and implementation will be complete by November 1st, 1994".

2.13.3 MB COMMENT

Very minor point.

HAMILTON

There were a number of further citations at the Hamilton inspection (19-22 Sept 1994; 38 Citations; Ms Erin Hyer) that were blood collection issues ie:

2.14.1 FDA CITATION

- #10. *At this site, nursing deferral codes are entered prior to any secondary review for accuracy/appropriateness*

2.14.2 CRC RESPONSE

"A Centre procedure for secondary review of nursing deferral codes prior to computer entry will be in place by September 30th, 1994".

2.14.3 MB COMMENTS

Minor point

2.15.1 FDA CITATION

- #12. *According to management, some donors are allowed to continue to donate, although there may be indications that they should have been deferred. The units from these donations are coded as "59" and are subsequently discarded*

2.15.2 CRC RESPONSE

"Currently any donor who passes all donor criteria including the health questionnaire, the interview and the confidential unit exclusion can donate blood. The "59" code was employed to provide a means for Centre personnel who were uncomfortable about a donor's suitability to have the unit destroyed. Effective September 23rd, 1994, use of this code was discontinued and a new procedure was introduced whereby donors who might fit in this category will be permanently deferred".

2.15.3 MB COMMENT

Minor point

2.16.1 FDA CITATION

- #21. *The SOP describing instructions for blood group determination done prior to donation does not specify how to make the determination for type "AB", nor gives adequate instructions on how to perform the rudimentary test*

2.16.2 CRC RESPONSE

"A National SOP has been developed and will be implemented prior to application for licensure".

2.16.3 MB COMMENT

Minor deficiency

2.17.1 FDA CITATION

#26. *Review of 20 plasmapheresis donor records revealed that 4 records do not contain a photo ID of the donor as required*

2.17.2 CRC RESPONSE

"Of the four records identified, three records were from donors who have not attended an apheresis clinic since 1993. In May 1994, the Centre purchased a camera and photos are being taken of all donors as they present themselves to the clinic".

2.17.3 MB COMMENT

Doubtful importance - plus is there a risk from identical twins if too much emphasis is placed on photograph ID?

2.18.1 FDA CITATION

i. **Saskatoon 26-27 Sept 1994. Ms Lisa Althar (9 Citations)**

#9 *Arm preparation procedures do not include a method and duration of a scrub technique, but only an application of Povidone-Iodine in an outward, circular pattern*

ii. **Regina 29-30 Sept 1994. Ms Lisa Althar (13 Citations)**

#11. *Arm preparation procedures do not include a method and duration of a scrub technique but only an application of Povidone-Iodine in an outward circular pattern followed by a 30 second dry time. In addition, an arm preparation was observed to be followed by only a 24 second dry time prior to venipuncture*

2.18.2 CRC RESPONSE

i. *"A double arm scrub in accordance with US FDA guidelines is in the process of being implemented and implementation will be completed by November 1st, 1994".*

ii. *"A double scrub procedure, in accordance with US regulations was implemented on October 3rd, 1994".*

2.18.3 MB COMMENT

These are minor non compliances.

2.19.1 FDA CITATION

Vancouver 26-30 Sept 1994. Ms Stephany Kersten (8 Citations)

- #2 *Of approximately 250 Health Assessment Questionnaires reviewed, 3 did not contain complete documentation of donor suitability*

2.19.2 CRC RESPONSE

"There errors occurred despite current check procedures including monthly random audit and routine review of the Health Assessment Questionnaires by a second clinic staff. Staff retraining has been initiated. A new procedure for a daily review of all Health Assessment Questionnaires was put in place to monitor the error trend and to assess the effect of the training program. In addition, the frequency of random audits will be increased. The three donors were contacted and all confirmed that there errors were clerical in nature and they were in good health and did not have any risk factors for AIDS".

2.19.3 MB COMMENT

This is a fairly important point and re-inforces a similar issue in our Winnipeg inspection. Perhaps reaches into the "major" area of concern.

2.20.1 FDA CITATION

Regina 29-30 Sept 1994. Ms Lisa Althar (13 Citations)

- #13. *There are no written procedures for documenting lot numbers and expiry dates of Povidone-Iodine swabs used for arm preparation prior to venipuncture*

2.20.2 CRC RESPONSE

"A procedure will be implemented within three weeks for documenting lot numbers of the Povidone-Iodine swabs".

2.20.3 MB COMMENTS

This is a minor matter of concern which was recorded in our Winnipeg report.

3. "COMPUTING"

3.1.1 FDA CITATION

- i. Toronto (#18) 18 -22 July 1994. Ms Mary Carden (19 Citations)
and
- ii. Halifax (#7) 12-14 Sept 1994. Ms Mary Carden (11 Citations)
and
- iii. Saint John (#1) 15-16 Sept 1994. Ms Mary Carden (10 Citations)
and
- iv. Hamilton (#18) 19-22 Sept 1994. Ms Erin Hyer (38 Citations)
and
- v. Saskatoon (#2) 26-27 Sept 1994. Ms Lisa Althar (9 Citations)
and
- vi. Regina (#3) 29-30 Sept 1994. Ms Lisa Althar (13 Citations)

There are no adequate systems in place to identify and correct duplicate donor records in the computer system

- vii. Vancouver 26-30 Sept 1994. Ms Stephany Kersten (9 Citations)

#8. *There are no procedures or programs in place to identify duplicated donor records in the (BLIS) computer system*

3.1.2 CRC RESPONSE

- i. Response to Toronto, Saint John, Hamilton and Regina Citations

"Our National (Toronto response stated current not National) computer system (BLIS) does not permit the identification and correction of duplicates. This is being addressed in current system enhancements. It is expected that a validated program will be in place by the end of the calendar year".

- ii. Response to Halifax, Saskatoon and Vancouver Citations

"This problem was recognised before the FDA inspection and program enhancements are being developed to prevent duplicate entries. It is expected to be in place before the end of the calendar year".

3.1.3 MB COMMENTS

This is an important point that was raised in our inspection reports. However, Centres had established (different) local procedures to deal with the matter.

The lack of an efficient, fully integrated computer system and the multiple problems with the existing system (BLIS) is a major cause for concern. Against this background it should be acknowledged that collection, testing and final release procedures were judged by the international team to be secure.

Indeed, numerous computing problems were identified in all of our inspections and feature collectively as a principal matter of concern for each inspection. There is sufficient concern in the cumulative points raised in the FDA reports to conclude that collectively (although not for each inspection) these would rank as a principal matter of concern. All computing problems listed hereafter will only receive a brief comment.

3.2.1 FDA CITATION

i. **Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)**

#19. *There are no written procedures in place for reporting computer system problems to National*

ii. **Regina 29-30 Sept 1994. Ms Lisa Althar (13 Citations)**

#4. *There are no written procedures for documenting error or problem reports with the computer system to ensure appropriate, timely corrective action*

3.2.2 CRC RESPONSE

i. **Response to Toronto Citation**

"The written procedure which was requested was available in the Centre (attached). It was, however, not located for review by the inspector. Separate logs of problems are maintained both in the Centre and at National Office".

ii. **Response to Regina Citation**

"The Centre will implement interim procedures within three weeks. National Computer Services will confirm in writing to a Centre when a problem is "closed". Nationally developed procedures will be reviewed and strengthened by National Computer Services within three months".

3.2.3 MB COMMENTS

i. Toronto Citation

If the procedure was available it clearly was not available when required (a GMP "rule") and staff were not familiar with the document. A minor problem.

ii. Regina Citation

A minor problem that re-inforces the view that error management needs to be improved.

3.3.1 FDA CITATION

i. Halifax 12 - 14 Sept 1994. Ms Mary Carden (11 Citations)

#11. *User documentation for computer services is inadequate*

ii. Saint John 15-16 Sept 1994. Ms Mary Carden (10 Citations)

#2. *User documentation from the BLIS system is inadequate*

3.3.2 CRC RESPONSE

i. Response to Halifax Citation

"This matter will be reviewed by National Computer Services and documentation improved where necessary. In addition, SOPs will be developed to cover all critical control points. This will be completed before application for licensure".

ii. Response to Saint John Citation

"Current user documentation for BLIS will be reviewed and strengthened by National Computer Services within three months".

3.3.3 MB COMMENTS

This is an important point that is difficult to assess ie what is the definition of "inadequate". On its own probably a minor deficiency. Interestingly, during our inspections individual Centres were each expending effort to produce their own users manual ie there was no National Co-ordination.

3.4.1 FDA CITATION

i. Saint John 15-16 Sept 1994. Ms Mary Carden (10 Citations)

#3. *Training records for the BLIS system are not adequate:*

- a. *there are no written procedures for training*
- b. *there are no written procedures for training updates*
- c. *there are no procedures in place for assessing the training performed and the adequacy of it*

ii. Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

#5. *There is no written procedure covering computer services training*

3.4.2 CRC RESPONSE

Response to Saint John and Hamilton Citations

"Written procedures for training, training updates, and assessment of training performed will be developed by National Computer Services and implemented within three months".

3.4.3 MB COMMENTS

Another important point. Probably, on its own, a minor deficiency.

3.5.1 FDA CITATION

i. Saint John 15-16 Sept 1994. Ms Mary Carden (10 Citations)

#4. *Training is performed on the live system using active records since no training or test database is available*

ii. Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

#6. *BLIS training is done "on line" system. There is no test data base*

iii. Saskatoon (#4) 26-27 Sept 1994. Ms Lisa Althar (9 Citations)

and

iv. Regina (#5) 29-30 Sept 1994. Ms Lisa althar (13 Citations)

Training of employees for computer system operations is performed on a live system using active records since no training or test data base is available

3.5.2 CRC RESPONSE

"An independent training database capability will be created by National Computer Services on a separate computer and implemented in three months. This will ensure that training does not occur on a live system".

3.5.3 MB COMMENT

This of itself is a minor deficiency. However, measures/procedures/records required to document and correct data errors during training would be a greater problem.

THE SAINT JOHN INSPECTION

A further 5 Citations referring to the BLIS system were made in Saint John by Mary Carden, these are as follows:

3.6.1 FDA CITATION

#6. *There are no logs of modem access to the system*

3.6.2 CRC RESPONSE

"All modem access to the computer system is automatically logged by BLIS. A procedure will be implemented to review the log and to document the purpose of each modem access. This procedure will be implemented within two months".

3.6.3 MB COMMENT

The CRC response implies the problem did not exist ie modem links were being logged, but goes beyond the citation to develop and implement an even better system.

3.7.1 FDA CITATION

#7. *Records of correction for duplicate donor records do not include information as to how the records were identified or how correct information for the donor was verified prior to deletion of one of the records*

3.7.2 CRC RESPONSE

"Documentation of duplicate donor records will be expanded to include the manner in which the duplicates were identified and verified prior to deletion of one of the records. The new documentation process will be implemented in three months".

3.7.3 MB COMMENT

This is a good point and once again reveals an opportunity for improving error management.

3.8.1 FDA CITATION

- #8. *There are no procedures for review by Quality Assurance of the program changes made as a result of faults in the system or problems identified in the BLIS system*

3.8.2 CRC RESPONSE

"Program changes which result from faults or problems in the system will be made by National Computer Services. The centre Quality Assurance Specialist will be notified of the program changes and will sign-off the implementation. The procedure will be implemented within three months".

3.8.3 MB COMMENT

This corrective action should bring an improvement in communication and GMP but of its own, the citation is not a major matter for concern in the CRC system.

3.9.1 FDA CITATION

- #9. *A complete investigation was not performed for BLIS problem log #9453. The record indicates Nursing and the Lab were informed to enter a 'one' in the Alert Duration when the field should be left blank*

3.9.2 CRC RESPONSE

"The incident referred to by the FDA inspector occurred on 4 February 1994. The incident was resolved but documentation of this incident was not completed according to standard practice. Proper documentation of Incident reports will be reinforced with the staff".

3.9.3 MB COMMENT

A minor GMP non compliance.

3.10.1 FDA CITATION

- #10. *Problem log #4802. The centre reported to National CRC on 1/10/92 a problem in DRM20. The program required the verification of data the operator identified as incorrect. The centre was informed the problem would be corrected, however, as of 9/16/94 no response has been received*

3.10.2 CRC RESPONSE

"The problem referred to by the FDA inspector was immediately corrected in accordance with documented procedures. The problem log was 'closed' in National Computer Services but was left 'open' at the centre. The inconsistency in the logs was not identified. National Computer Services will confirm in writing to a centre when a problem is 'closed'".

3.10.3 MB COMMENTS

Suggests a minor systems failure, primarily at Saint John.

3.11.1 FDA CITATION

i. London 19-21 Sept 1994. Ms Sandra White (4 Citations)

- #3. *Review of written procedures re: the BLIS and/or BCI computer database system(s) found no written procedure exists which defines/indicates access authorisation and/or restrictions to programs*

3.11.2 CRC RESPONSE

"The Centre is developing written procedures that define access authorisation and/or restrictions to programs. This will be implemented by 30 September 1994".

3.11.3 MB COMMENT

An important point, possibly ranks in the major category but difficult to be sure without all relevant details (see also 3.5.3).

HAMILTON

19-22 Sept 1994. Ms Erin Hyer (38 Citations)

A further 4 Citations on BLIS/computing, these are as follows:

3.12.1 FDA CITATION

- #4. *No validation of the computer system BLIS software and hardware is done by site computer personnel, including when new procedures are implemented*

3.12.2 CRC RESPONSE

"Changes to BLIS software, hardware and procedures are controlled and tested by National Office. Procedures for the verification of the implementation of these changes by site personnel and the Quality Assurance Specialists will be developed and implemented within the next three months".

3.12.3 MB COMMENTS

The systems seem to be adequately validated. What seems to be lacking is Centre Control through QA to ensure implementation does not take place until appropriate.

3.13.1 FDA CITATION

- #7. *This site uses an automated "sort" software program for final product labelling and release for use. There are no written training procedures for "Sort", and employees are not trained with test data, but rather "on-line"*

3.13.2 CRC RESPONSE

"Current user documentation and training procedures will be reviewed by National

Computer Services and strengthened over the next three months".

3.13.3 MB COMMENT

This of itself is a minor deficiency. However, measures/procedures/records required to document and correct data errors during training would be a greater problem.

3.14.1 FDA CITATION

- i. #8. *There are no written procedures describing how to perform manual operations when the computer systems are inoperable*
- ii. Saskatoon 26-27 Sept 1994. Ms Lisa Althar (9 Citations)
 - #3. *There are no procedures for reverting to manual procedures or delaying operations when the computer system is not functioning or is backing up during the working day*

3.14.2 CRC RESPONSE

- i. *"Procedures for manual operations when BLIS is inoperable will be developed by National Computer Services within three months. A written procedure describing manual sorting is in place as a backup to the automated sorting system (which is Nationally approved) used in the Centre".*
- ii. *"Procedures for manual operations when BLIS is inoperable will be developed by National Computer Services within three months".*

3.14.3 MB COMMENT

An important point but the schedule for development/implementation should be viewed against the frequency of computer system. (My impression was that the hardware was fairly robust but was old and used outdated (and slow) operating systems).

3.15.1 FDA CITATION

- #9. *No National SOP covering verification of computer deferral code entry exists*

3.15.2 CRC RESPONSE

"A National SOP covering verification of computer deferral codes will be developed and implemented within the next three months".

3.15.3 MB COMMENT

An important point but probably of its own a minor GMP non compliance.

3.16.1 FDA CITATION

Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

- #11. *There are no written procedures which fully define what the deferral codes reference*

3.16.2 CRC RESPONSE

"The Nursing deferral codes are referenced in the Donor Selection Criteria Manual (National SOP). Laboratory TD codes are linked to test results entered by the laboratory technologist (QA:223 Version 5). A written procedure fully defining the codes (Table Master) and their use will be developed in the Centre".

3.16.3 MB COMMENT

Minor GMP non compliance.

4. "TRANSMISSIBLE DISEASE SCREENING"

4.1.1 FDA CITATION

No testing for anti-HBc

- i. Toronto (#4) 18-22 July 1994. Ms Mary Carden (19 Citations)
and
- ii. Edmonton (#3) 19-21 Sept 1994. Mr Ronnie E Jackson (10 Citations)

Blood products are not tested for Hepatitis B Core antigen (anti-HBc)

- iii. Winnipeg 19-22 Sept 1994. Ms Alice Krivitsy (9 Citations)

#1. *Hepatitis B core (anti-HBc) testing is not done on the blood collected from allogeneic and autologous whole blood and platelet pheresis donors*

4.1.2 CRC RESPONSE

The CRC made an identical response to all 3 citations. ie

"Testing of blood products for transfusion for anti-HBc is not a regulatory requirement in Canada. It is our understanding that plasma for further manufacturing does not have to be tested for anti-HBc".

4.1.3 MB COMMENT

The CRC comment is absolutely correct and, I feel, FDA inspectors have made an error in citing this observation.

Anti-HBc screening was introduced in some countries as a surrogate test for "non A non B hepatitis "(not UK although it was given very serious consideration). Since high quality anti-HCV screening kits (3rd Generation used in UK) have been developed, many consider anti-HBc screening does not make best use of available funds. Some countries who currently screen for anti-HBc are considering abandoning the test.

Anti-HBc screening also brings problems ie donors repeatably reactive for anti-HBc must then be tested for anti-HBs. If the donor has anti-HBs of a sufficient (arbitrarily defined) potency, then the donation can be used. Obviously, this is the reverse of what normally happens in transmissible disease screening and, to be done properly, would require establishment and maintenance of a National anti-HBs standard for calibration purposes.

The CRC/BoB should establish whether Canada needs to undertake anti-HBc screening as a surrogate test or whether the introduction of anti-HCV 3rd generation would be a more effective policy.

Finally, and this is a very minor point, the words "Hepatitis B core antigen" are used in the citation from Toronto. Clearly, this is an error (antibody should have been used) but was repeated word for word in the citation from Edmonton some 2 months later.

4.2.1 FDA CITATION

i. **Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)**

#6. *There are no procedures for quarantine and retrieval of in-date units from prior collections for donors having repeatedly reactive screening tests for antibodies to HIV*

ii. **Vancouver 26-30 Sept 1994. Ms Stephany Kersten (8 Citations)**

#6. *There are no procedures in place for the retrieval and quarantine of in-date products of previous donations from donors who test repeatedly reactive for anti-HIV*

4.2.2 CRC RESPONSE

i. **Response to Toronto Citation**

"The current practice in Canada is to retrieve in-date units from prior collections following a confirmed positive test for antibodies to HIV (SOP CQ/1070, Section 6.1.1). We are revising our SOP to comply with the FDA Guideline of April 1992. This will be implemented prior to our application for an FDA licence".

ii. **Response to Vancouver Citation**

"As indicated previously, we are revising our SOP (SOP CQ/1070, Section 6.1.1) to comply with the FDA Guideline of April 1992. This new procedure will be implemented prior to our application for an FDA licence".

4.2.3 MB COMMENTS

I was contacted about this issue before my visit by Dr Kennedy in Ottawa and asked to give the SNBTS position. In fact we do not comply with this FDA guideline. However, I think the FDA have made a good point. I have raised this issue with our SNBTS Medical and Scientific Committee and have been asked to explore the possibilities and problems of introducing such a policy (for HBsAg, anti-HIV 1+2 and anti-HCV repeat reactive, previously negative donors). We will also look at frozen red cell donations.

4.3.1 FDA CITATION

Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

- #12. *There are no procedures for calibration (sample volume) for the Hamilton-Integra used in transmissible disease testing*

4.3.2 CRC RESPONSE

"Each Centre has the Sanofi protocol which describes these calibration procedures. The Red Cross has a contract with the manufacturer for the calibration to be performed quarterly or as needed. A copy of the calibration report is left and filed with each centre upon completion".

4.3.3 MB RESPONSE

From our experience, each of the 3 sites undertook regular verification of dispense volume based on a National procedure. If this was not being done in Toronto it is not an important safety issue but a minor GMP non compliance.

4.4.1 FDA CITATION

- i. Toronto (#13) 18 -22 July 1994. Ms Mary Carden (19 Citations)

and

- ii. Halifax (#2) 12-14 Sept 1994. Ms Mary Carden (11 Citations)

and

- iii. Hamilton (#26) 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

Test procedures for transmissible disease testing each require specific parameters for determining validity of the test runs. There are no records to demonstrate the software is properly determining the validity of test runs

4.4.2 CRC RESPONSE

- i. Response to Toronto Citation

"We have been informed by Genetic Systems Corporation that the software used at the Red Cross Centres has been submitted to the FDA via pre-market notification (510k) route. A complete software validation including limits testing was performed and is on file at Genetic Systems. After installation of each assay and prior to training, a software verification was performed at each Centre. The software verification confirms the validity of the test runs

by comparing the cut-off calculation and mean of the Positive and Negative Controls with those calculated manually. These results are retained at each Centre.

The parameters cannot be changed as with other kits which, provides for additional security".

ii. Response to Halifax and Hamilton Citations

"The software used has been fully validated by the manufacturer and approved by the FDA. The test kit and associated software underwent a verification procedure at National Office and, in addition, data from parallel testing in Centres were submitted to the Canadian regulatory agency for their approval (as per their requirement) before it was accepted as a test-of-record.

While our verification procedure stress tests many possible scenarios, a more complete protocol is being developed with the manufacturer to properly determine the validity of the test runs. This will be completed in 60 days. (Halifax response mentions: .. within the next 2 months, not 60 days)".

4.4.3 MB COMMENTS

It is not clear why this has been cited. The CRC response of 12 Sept 1994 to the FDA provides adequate evidence that the CRC were acting efficiently on this matter. Therefore, it is surprising that FDA inspectors have cited this as a non compliance and that the same non compliance was recorded after receiving the CRC response.

(Response received 12 Sept 1994, citation repeated 12-14 Sept 94 in Halifax [same investigator], 19-22 Sept 1994 in Hamilton [different investigator]).

4.5.1 FDA CITATION

Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#15 *Traceback cases are closed after the first positive donor has been identified. The test results for suspect blood products are not reviewed in all cases as stated in the National Directive*

4.5.2 CRC RESPONSE

"It has been identified that the current SOP (QA:75) required revision to reflect actual current practice. The current practice requires that all donors in a traceback case are sent a notification letter. If a positive donor is found, further investigations are not pursued. Procedures are now being developed to follow up all donors.

4.5.3 MB COMMENTS

This was one of two items in a telephone inquiry I received prior to my visit from Dr Kennedy in Ottawa (to establish SNBTS position). Whilst statistically it is extremely unlikely that more than one donor would be positive for transmissible disease markers, all donors must be checked. In Scotland, we have archive serum samples for all donations collected since about 1986 and in such instances the archive samples are retrieved and tested. This is not standard practice in Canada. The FDA are correct, all donors implicated in such a situation should be traced. The odds might be extremely slim but if eg a recipient contracted HIV after transfusion and of the red cells transfused, 2 came from sexual partners, if only one were identified (as per the apparent procedure in Toronto), then components from the second donor, also infective for HIV may be left in inventory (eg frozen red cells).

This probably would be ranked as a principal matter of concern.

4.6.1 FDA CITATION

- i. **Halifax (#1) 12-14 Sept 1994. Ms Mary Carden (11 Citations)**

and

- ii. **Hamilton (#2) 19-22 Sept 1994. Ms Erin Hyer (38 Citations)**

The procedure used for HBsAg testing includes the use of a "mix mode " during the 37° incubation steps (contrary to) the manufacturers' directions for use (which) do not provide for the use of a mix mode*

()* = omitted in Hamilton Citation

- iii. **Saskatoon (#1) 26-27 Sept 1994. Ms Lisa Althar (9 Citations)**

and

- iv. **Regina (#1) 29-30 Sept 1994. Ms Lisa Althar (13 Citations)**

The Centre's written procedure used for HBsAg testing includes the use of a shaker incubator at mix speed 1 during the 37°C incubation. The manufacturer's directions for use do not provide for mixing during incubation

4.6.2 CRC RESPONSE

Response to Halifax, Hamilton, Saskatoon and Regina Citations

"The 'mix mode' refers to the use of a shaking incubator. Although this method has been proven to increase the sensitivity of the assay and accepted by the Canadian regulatory agency, it is not documented in the product insert. The manufacturer will apply to the FDA for approval of this method".

4.6.3 MB COMMENTS

CRC are quite correct, "shaking incubation" does produce an increase in the sensitivity of HBsAg tests. We call it "dynamic incubation" and have validated the improvement and use this routinely. This method is not on the insert presumably because the kit is an FDA licensed product. It could take many months for FDA approval!

HALIFAX

A further 5 Citations were made by Ms Mary Carden at the Halifax inspection (12-14 Sept 1994, 11 Citations). All were related to transmissible disease screening ie:

4.7.1 FDA CITATION

#3. *SOP QA223 Version 3 (effective 9/90 to 11/91) and Version 4 (effective 11/91 to 4/92) provides for interpretation of Western blot patterns for HIV-1 to be interpreted as negative with p17 and p70 bands present when the product insert indicates negative Western blot patterns have no bands present*

4.7.2 CRC RESPONSE

"The interpretation of the Western blots were based on the recommendations of a WHO Expert Committee who deemed that p17 bands alone were to be interpreted as negative. Bands at p70 were considered to be non-viral bands having no specificity for viral proteins.

Effective immediately, we will comply with package insert criteria in interpreting Western blots for manufacturing purposes, but will continue to retain current WHO interpretation for purposes of counselling donors".

4.7.3 MB COMMENT

#3 CRC are following an international convention - the deficiency cited relates to not following FDA regulations/manufacturers insert. Published work has shown that 20% of anti-HIV ELISA screen negative 'normal' donors have one or more non specific band on western blot. (Genesca et al, Lancet, 1023-1025; October 28 1989.)

4.8.1 FDA CITATION

- #4. *SOP QA223 Version 4 (effective 11/91 to 4/92) allowed re-entry of donors who were Western blot indeterminate for HIV*

4.8.2 CRC RESPONSE

"Donor who have been re-entered using this protocol will be deferred".

- 4.8.3 #4 There is insufficient detail to comment authoritatively. eg the anti-HIV Elisa status of the re-entered donor is not given, nor is there any information on the actual process of establishing re-entry ie the time period between the index Western blot result and the follow-up Western blot/Elisa tests or of the bands viewed.

4.9.1 FDA CITATION

- #5. *SOP QA223 Version 3 allowed re-entry of donors for HBsAg without anti-HBc testing being performed on the sample repeatedly reactive for HBsAg*

4.9.2 CRC RESPONSE

"SOP QA223 Version 3 did not clearly reflect the actual practice of the National Reference Laboratory, which included anti-core testing of all reactive samples which were not confirmed to be positive by neutralisation assay (in accordance with FDA memorandum dated December 2, 1987). The Centre has reviewed all relevant files from that period and have confirmed that the procedure described above has been followed in all cases".

- 4.9.3 #5 The CRC response is adequate but they should check the matter raised in this citation has been dealt with for all Centres and should document this action.

4.10.1 FDA CITATION

- #6. *SOP QA223 Version 3 did not provide for permanent deferral of donors for HTLV-1 after two repeatedly reactive test results in a time period greater than six months*

4.10.2 CRC RESPONSE

"As of November 1991 (SOP QA223 Version 4), all donors repeat reactive for HTLV-1 are permanently deferred".

4.10.3 MB COMMENT

Very hard to comment without viewing the documentation. However, the point being made in the Citation seems to be that any donors who gave two repeatedly reactive test results in a time period greater than six months when QA223 version 3 was current were not permanently deferred.

I have insufficient info to comment on the seriousness of this omission (we don't test for anti-HTLV I/II) but an effective "close out" could be achieved by checking records to establish whether any such donors have not been deferred.

HAMILTON

A number of other Citations made in the Hamilton inspection (19-22 Sept 1994, 38 Citations, Ms Erin Hyer) were related to transmissible disease testing ie:

4.11.1 FDA CITATION

- #3. *Only a 70 day previous donation inventory retrieval is done for units from donors testing repeatedly reactive for HBsAg*

4.11.2 CRC RESPONSE

"The Red Cross revised this SOP in August 1992 to extend the inventory retrieval period to 6 months. Hamilton Centre was in compliance with this SOP. The update had not been inserted in the copy of the SOP reviewed by the inspector. This has been corrected.

This will be discussed at a National training session for Quality Assurance Specialists that will take place during the week of October 17th, 1994 as previously planned".

4.11.3 MB COMMENT

A minor deficiency which indicates that document control is not secure.

4.12.1 FDA CITATION

- #31. *Review of Lookback files (52-94-004) revealed that for donation date 1/26/94, it was noted that there may be "...possible carryover on Hamilton AT ..". The site investigation of this incident is not contained within this file*

4.12.2 CRC RESPONSE

"We file each incident investigation according to the lead department. In this case the carry-over investigation report (led by laboratory) was filed separately from the lookback investigation (led by quality assurance). We have now photocopied the carry-over file and placed it with the lookback file.

This issue will be discussed at a National training session for Quality Assurance Specialists that will take place during the week of October 17th, 1994 as previous planned".

4.12.3 MB COMMENT

A very minor point of detail.

4.13.1 FDA CITATION

- #32. *The results of the investigation done by National for the possibility of carryover for the Hamilton AT were not transmitted to this site until 9/21/94*

4.13.2 CRC RESPONSE

"Hamilton Centre reported the first incident of carry-over to National Office in April 1993. The investigation by National Office led to a change in pipetting routine for repeat testing. This routine was introduced in all Centres by Sanofi starting the week of August 9th, 1993 and was completed by the week of August 23rd, 1993. A reference for this action was forwarded on request on September 21st, 1994.

This issue will be discussed at a training session for Quality Assurance Specialists that will take place during the week of October 17th, 1994 as previously planned".

4.13.3 MB COMMENT

The CRC response indicates a lack of communication.

4.14.1 FDA CITATION

#33. There is no written procedure explaining how to investigate possible carry-over, how to retest these donors for possible re-entry as donors, or how to report this type of incident to National

4.14.2 CRC RESPONSE

"National Office will revise the SOP for HBsAg testing to address this issue within the next two months".

4.14.3 MB COMMENT

A minor deficiency point.

4.15.1 FDA CITATION

#35. The site SOPs regarding the Hamilton Integra AT automatic pipettor are all DRAFT and not approved

4.15.2 CRC RESPONSE

"Centre procedures for the Integra AT were approved and signed off on September 23rd, 1994".

4.15.3 MB COMMENT

Minor deficiency.

4.16.1 FDA CITATION

#36. National SOP QAI70 does not accurately reflect the equipment currently in use at all CRC sites for viral disease testing. This SOP discusses the monitoring of kit performance for the DuPont anti-HIV test kit and the Abbott Auszyme HbsAg test kit. The CRC Centres use the Genetics Systems kit for HIV and HBsAg testing and the Ortho kit for HCV testing

4.16.2 CRC RESPONSE

"This National SOP will be revised to address this issue within the next two months".

4.16.3 MB COMMENT

Minor deficiency.

4.17.1 FDA CITATION

#38. *On 9/19/94, observed that unapproved SOPs were in place on the Hamilton automatic pipettor and on the EL 312e microplate Bio-Kinetics reader*

4.17.2 CRC RESPONSE

"The two unapproved SOPs were removed from the Laboratory on September 19th, 1994, immediately after the investigator's observation. Only approved Centre procedures are in place at this time.

A National training session on document control for Quality Assurance Specialists will take place during the week of October 17th, 1994 as previously planned".

4.17.3 MB COMMENTS

Minor deficiency.

VANCOUVER

A number of other Citations made in the Vancouver inspection (26-30 Sept 1994; 8 Citations; Ms Stephany Kersten) were related to transmissible disease screening ie

4.18.1 FDA CITATION

#3. *Personnel performing weekly volume verification of the Ortho Summit and personnel reviewing the Ortho Summit volume verification report dated 9/20/94 (for serial number 1033.048) did not note values deviated from manufacturer's specification*

4.18.2 CRC RESPONSE

"The validity of the test was not compromised as these values are not used for verification, however, the importance of a complete review of data has been re-emphasised. A revised training program which included volume verification was instituted immediately and given to the staff. A copy of the program was given to the inspector".

4.18.3 MB COMMENT

A minor GMP deficiency.

4.19.1 FDA CITATION

- #4. *Personnel performing weekly volume verification of the Ortho Summit 8/25/94 to the present failed to enter the calibrated value of the manual pipette utilised to perform volume verification. The manual pipette was calibrated to deliver an actual volume of 99.89 on 8/25/94. Volume verification reports dated after 8/25/94 indicate a value of 101.5 was utilised to perform weekly volume verification*

4.19.2 CRC RESPONSE

"The validity of the tests were not compromised because all test and control ranges had met the manufacturer's specifications. Test results since 8/25/94 were recalculated using the correct value.

The following corrective action was also immediately taken. A revised Volume Verification Log was developed to include a sign-off that calibration values are recorded and included on all volume verification report calculations. A re-training program was conducted with staff on the use of this new form and the requirement to ensure that the correct calibration value is used for calculations".

4.19.3 MB COMMENT

A minor deficiency.

4.20.1 FDA CITATION

- #5. *The manufacturer's operator's manual for the Ortho Summit requires the use of a direct-displacement pipette for weekly volume verification. It has not been determined that the Gilson Pepetman in use for weekly volume verification of the Ortho Summit is a direct-displacement pipette*

4.20.2 CRC RESPONSE

"A recent memo from the manufacturer (attached) confirmed that it is an acceptable practice to use an air-displacement pipette which has been gravimetrically calibrated (current practice of the Centre). Unfortunately, this was not available for reference at the time of the inspection".

4.20.3 MB COMMENT

A minor deficiency.

5. "COMPONENT PRODUCTION, LABELLING, STORAGE AND RELEASE"

Blood components have no expiry date on the label

5.1.1 FDA CITATION

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#3. *Blood products are labelled with the collection date and no expiration date*

ii. Edmonton 19-21 Sept 1994. Mr Ronnie E Jackson (10 Citations)

#4. *Blood products are labelled with collection date only and no date of expiration*

iii. Winnipeg 19-22 Sept 1994. Ms Alice Krivitsy (9 Citations)

#3. *A collection date rather than an expiration date is used when labelled blood products*

iv. Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

#19. *Blood products are only labelled with the collection date. The expiration date is not present*

5.1.2 CRC RESPONSE

i. Response to Toronto, Edmonton and Hamilton Citations

"Source plasma will be labelled with the expiration prior to our application for a US licence.

It is our understanding that an expiration date is not required on recovered plasma".

ii. Response to Winnipeg

"SOPs which meet FDA guidelines will be developed and implemented prior to applying for US licensure".

5.1.3 MB COMMENT

This is an important issue that needs to be addressed very carefully. (see the international team audit reports for Saint John and especially Winnipeg). The principal concern relates to the extent to which those who are involved in administration of blood and its components (eg anaesthetists) are aware of such matters. As an aside, in the UK there is an assumption that if anticoagulants/additives

include adenine, red cell components have a 35 day shelf life. However, in the UK one manufacturer of blood packs that contain an anticoagulant with adenine in the formulation have a licence for only 28 days storage ie presumptions can be misleading.

It is international practice to indicate clearly the date when any medicinal product expires. The convention (at least in Europe) is that an expiry date of MM/YY represents one minute to midnight on the last day of the month and that an expiry date of DD/MM/YY represents expiry on midnight of the date notified.

5.2.1 FDA CITATION

Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

- #11. *Autologous blood procedures do not require the "For Autologous Use Only" label in place of the blood group label for donors who do not meet all donor suitability criteria*

5.2.2 CRC RESPONSE

"As indicated above, all shipments of autologous blood to the United States have been discontinued".

5.2.3 MB COMMENTS

This represents a difference in Canadian and US practice. Without knowledge of what suitability criteria were not met it is difficult to comment whether this is an important safety issue.

SUDBURY

There were two further citations at the Sudbury inspection (12-14 Sept 1994; 5 citations; Ms Sandra White) that were "storage" issues ie:

5.3.1 FDA CITATION

- #4. *Stacked plastic trays containing acceptable ABO/Rh+ blood products which were stored in the laboratory walk-in refrigerator and available for release/distribution, lacked conspicuous identification by blood type (Positive Rh)*

5.3.2 CRC RESPONSE

"This citation arose because the Centre had labelled the shelves for released Rh

negative red cells with a "NEGATIVE" sign, but had not labelled the shelves for Rh positive units. A sign was put up before the FDA investigator left the Centre".

5.3.3 MB COMMENTS

This is a very minor GMP issue (ie lack of Status Labelling).

5.4.1 FDA CITATION

#5. *Blood/blood products are not visually inspected on a daily or periodic basis, ie during daily inventory check, and the activity is not indicated or addressed in written procedures*

5.4.2 CRC RESPONSE

"In the immediate term, the Centre will implement a procedure which will require visual inspection to be conducted and documented when inventory checks are performed. Retraining of staff will be done and documented on a sign-off sheet. A record of all visual inspections will be kept on file. National Office has developed an SOP to implement this procedure which will be in place in all Centres before applying for licensure".

5.4.3 MB COMMENT

This seems to me to be unnecessary. Blood bank fridges tend to have less than optimal lighting for such an activity. If a thorough visual inspection is part of the pre-issue routine, surely this is adequate.

5.5.1 FDA CITATION

Windsor 19 Sept 1994. Ms Sandra White (3 Citations)

#3 *Review of temperature recording charts for 1994 revealed:*

- a. *failure to explain/document recording gaps re: the Puffer-Hubbard refrigerator charts for weeks 06/07/94, 06/13/94, 06/20/94, and 06/27/94; and*
- b. *several Harris freezer charts similarly lacked explanation/documentation re: recording gaps*

5.5.2 CRC RESPONSE

- "a. *An hourly manual record of temperature was instituted to replace a malfunctioning chart recorded. Documentation of the manual record substitution was inadvertently omitted from the continuous recording chart. A training session has been held with staff to reinforce the importance of*

documenting the reason for gaps in recordings.

- b. *The episodes occurred in weeks containing "Monday" statutory holidays. The normal procedure is to install new charts on Mondays, but when there is a Monday statutory holiday charts are installed on Tuesdays. This result in a six (6) day chart for the week in question. Documentation of the "short" week was inadvertently omitted from the charts. Recorder chart replacement has now been rescheduled to prevent the occurrence of gaps. A training session has been held with staff to reinforce the importance of documenting the reason for gaps in recordings".*

5.6.1 FDA CITATION

London 19-21 Sept 1994. Ms Sandra White (4 Citations)

- #4. *Doors to the front of the refrigerated walk-in storage unit (as opposed to the rear end) lacked conspicuous identification for the blood supply deemed acceptable/suitable for distribution. This blood supply is accessible from both the front and rear ends of the storage unit*

5.6.2 CRC RESPONSE

"Corrective action was taken prior to the departure of the Inspector. A conspicuous sign "tested units behind glass door", has been affixed to the front of the walk-in refrigerator".

5.6.3 MB COMMENTS

These are fairly typical, minor GMP non-compliances, various examples of which occur in our reports.

HAMILTON

There were three further citations at the Hamilton inspection (19-22 Sept 1994; 38 Citations; Ms Erin Hyer) that were "component" issues ie:

5.7.1 FDA CITATION

- #13. *Prior to 9/21/94, plasma for fractionation which has been quarantined is not stored separately from acceptable plasma. Initially reactive units remained in the firm's "Untested Plasma for Fractionation" freezer*

5.7.2 CRC RESPONSE

"Prior to 9/21/94, quarantined plasma was stored separately from acceptable (ie released) plasma for fractionation. It is true, however, that initially reactive units

were not segregated from untested units. The Centre has created a separate area to contain initially reactive plasma components. This was done within six hours of the inspector's observations".

5.7.3 MB COMMENTS

The notion of quarantining initially reactive frozen plasma donations was something we explored in our inspections. Operationally it was easier to leave the plasma there until repeat testing was done. From a safety point of view the procedures viewed were secure but from a GMP perspective you would wish to quarantine "initially reactive" plasma donations.

5.8.1 FDA CITATION

#14. *On 9/19/94, tested and released units of plasma suitable for shipment to the US were stored in the "Untested Plasma for Fractionation" freezer*

5.8.2 CRC RESPONSE

"Released units were moved into the "tested plasma for fractionation" freezer on September 19th, 1994 within 6 hours of the investigator's observation".

5.8.3 MB COMMENT

Without having access to further information or a proper context, it is difficult to assess the level of safety risk here. At worst, I consider it to be a major GMP non compliance. However, it is not known what procedures were in place to control release of product to the fractionator, and to prevent "untested" boxes of plasma to be sent to the fractionator. If these are secure there would only be a very small safety risk.

5.9.1 FDA CITATION

#27. *This site is using quad whole blood units which are already prelabeled as "Rh pos". Current procedure is to apply a "Rh neg" or "Rh pos" sticker over the label*

5.9.2 CRC RESPONSE

"The Centre will replace the current stock of pre-labelled and quad packs with new unlabelled stock. The exchange will be completed within the next three weeks".

5.9.3 MB COMMENT

This is an important GMP point but probably not a safety issues. More detail would be needed to comment authoritatively.

5.10.1 FDA CITATION

#28. *Component labels are placed on the satellite bags prior to the completion of component preparation*

5.10.2 CRC RESPONSE

"This issue has been addressed in the new National SOPs which will be implemented before application for licensure".

5.10.3 MB COMMENT

Minor GMP non compliance.

5.11.1 FDA CITATION

#29. *There is no written procedure describing the component preparation of "cryosupernatant" product which can be shipped as plasma for further manufacturing use*

5.11.2 CRC RESPONSE

"There are written procedures (SOP LS:209, LS:205) describing the preparation of "cryoprecipitate supernatant plasma". There is no procedure for application of the attribute label "cryosupernatant". Use of this label has been discontinued until National procedures have been written and implemented".

5.11.3 MB COMMENTS

This is a minor GMP non compliance.

SASKATOON

There were two further citations in the Saskatoon inspection (26-27 Sept 1994, 9 Citations, Ms Lisa Althar) that were "component" issues ie.

5.12.1 FDA CITATION

#6. *The approved written procedure for calibration of the Sorvall RC-3B centrifuges used for the preparation of recovered plasma does not include acceptable ranges or method of corrective actions that should be conducted for results that are out-of-range*

5.12.2 CRC RESPONSE

"A Centre Operating Procedure for calibration of the centrifuge will be developed and implemented by October 24th, 1994. A National agreement with the manufacturer has been completed for periodic calibration, and calibration after repairs, of their equipment".

5.12.3 MB COMMENT

Minor GMP non compliance.

5.13.1 FDA CITATION

- #7. *There is no written procedure for calibrating scales used in the preparation of recovered plasma*

5.13.2 CRC RESPONSE

"A Centre Operating Procedure for calibrating scales will be developed and implemented by October 24th, 1994. New certified weigh scales (including calibration procedures) are presently being introduced at all Centres. Implementation will be completed before applying for licensure".

5.13.3 MB COMMENTS

Minor GMP non compliance.

5.14.1 FDA CITATION

Regina 29-30 Sept 1994. Ms Lisa Althar (13 Citations)

- #9. *An out-of-range temperature between -16°C and -17°C observed for Freezer #1 temperature recording chart dated 4/12-17/94 was not explained as required in COP EQ 207*

5.14.2 CRC RESPONSE

"The incident in question was confirmed to coincide with a shipment of plasma for fractionation from the freezer. Staff will be retrained on proper procedures for documenting out-of-range temperatures".

5.14.3 MB COMMENTS

This is a minor GMP non compliance.

6. "TRAINING"

6.1.1 FDA CITATION

i. Saint John 15-16 Sept 1994. Ms Mary Carden (10 Citations)

#5. *There are no training records for all employees with access to programs in the BLIS system*

ii. Edmonton 19-21 Sept 1994. Mr Ronnie E Jackson (10 Citations)

#9. *Computer training documentation for personnel assigned to the computer services department is not documented in their training records*

See also #3.4 and #3.5

6.1.2 CRC RESPONSE

Response to Saint John and Edmonton Citations

"While all employees with BLIS access have been trained, the documentation of the training was found to be incomplete by the FDA inspector. (Consistent with our response to observation number '3', all training records will be standardised and updated)".*

()* = omitted from Edmonton response

6.1.3 MB COMMENT

An important point but a minor GMP non-compliance.

6.2.1 FDA CITATION

Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

#37. *The SOP used by the laboratory for training is an unapproved copy of a National DRAFT SOP from 1992. There is no indication that the procedure has been approved by anyone at National level or at the site*

6.2.2 CRC RESPONSE

"This issue has been addressed in the new National SOPs which will be implemented before application for licensure".

6.2.3 MB COMMENT

This is a minor GMP non compliance.

6.3.1 FDA CITATION

i. **Saskatoon 26-27 Sept 1994. Ms Lisa Althar (9 Citations)**

#5. *There is no documentation of training for the Laboratory Manager or Computer Services Supervisor to show they have received specific training in the operations they supervise*

ii. **Regina 29-30 Sept 1994. Ms Lisa Althar (13 Citations)**

#6. *There is no documentation that training for the Computer Services Supervisor has ever been assessed. The Computer Services Supervisor has signed training records as both the employee and supervisor*

iii. #7. *There is no documentation that the Laboratory Manager has received specialised training in laboratory equipment/operations as required in the job description.*

6.3.2 CRC RESPONSE

i. *"National procedures are being developed for the documentation of training of regulated job responsibilities. These procedures will include and specify the appropriate qualifications and training requirements for Laboratory Managers and Computer Services Supervisors and will be implemented before applying for licensure".*

ii. *"Written procedures for training, training updates, and assessment of training performed will be developed by National Computer Services and implemented within three months".*

iii. *"A documented training plan for management personnel will be developed and implemented nationally prior to application for licensure".*

6.3.3 MB COMMENTS

Without seeing the job descriptions it is difficult to comment authoritatively. However, these are not major points of concern and are issues that are exercising the minds of many organisations, not least the SNBTS.

7. "QA"

7.1.1 FDA CITATION

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#14. *All local procedures developed for implementing National directives are not dated and signed as approved*

ii. Halifax 12-14 Sept 1994. Ms Mary Carden (11 Citations)

#10. *All local procedures developed for implementing National directives are not dated and signed as approved. For example, SOPs for computer services, deferral codes and equipment calibration*

7.1.2 CRC RESPONSE

i. Response to Toronto Citation

"Centre procedures relating to National Directives will be dated and signed".

ii. Response to Halifax Citation

"Centre operating procedures will be developed to ensure that there is proper documentation (date, sign-off) showing that all operating procedures have been properly approved by the Medical Director. For equipment calibration, this was identified as a human resource problem and the National Director has agreed to the approval of a new position for a dedicated expert to be put in charge of this area. This position will be approved and the hiring process initiated within one month".

7.1.3 MB COMMENTS

This is a minor GMP non-compliance and reflects the view expressed in our reports that appreciation of GMP has not yet reached an adequate level.

7.2.1 FDA CITATION

i. Toronto 18 -22 July 1994. Ms Mary Carden (19 Citations)

#16. *All records for error/incident reports do not include identification of how the problem was identified, a record of the investigation, conclusion and follow-up*

ii. **Halifax 12-14 Sept 1994. Ms Mary Carden (11 Citations)**

#9. *Quality Assurance does not have a mechanism in place to track and analyse errors or problem reports to ensure appropriate timely corrective action. At least nine problem reports between May 1994 and August 1994 indicate health assessment questionnaires were incomplete yet corrective action was not implemented until September 1994*

iii. **Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)**

#16. *There is no National SOP regarding error/accident reporting*

#17. **REVIEW OF THE ERROR/ACCIDENT FILES AT THIS SITE REVEALED NUMEROUS DEFICIENCIES INCLUDING INCOMPLETE RECORDS, POOR CATALOGUING OF REPORTS, AND FOR SOME FILES, LACK OF THE "DEPARTMENTAL INCIDENT/ERROR REPORT" WHICH DOCUMENTS ANY CORRECTIVE ACTION, ACTION TO PREVENT REOCCURENCE, REPORT OF INCIDENT TO THE MEDICAL DIRECTOR, AND REPORT OF INCIDENT TO THE NATIONAL OFFICE**

7.2.2 CRC RESPONSE

i. **Response to Toronto Citation**

"Error/incident reports which are required to be reported to National Office contain the above information. The majority of the reports in the centre were properly documented however, documentation requirements have been re-enforced with centre staff".

ii. **Response to Halifax Citation**

"This has been identified as a human resource problem. It will be evaluated by the Centre and a report submitted to National Office in two weeks. The National Director has agreed to expeditiously review the proposal and provide the necessary resources. This position will be approved and the hiring process initiated within one month".

iii. **Response to Hamilton Citation #16**

"A National SOP for error/accident reporting is being developed and will be implemented prior to application for licensure".

iv. **Response to Hamilton Citation #17**

"The complete review of all Error/Accident files will be completed by September 30th, 1994. A Centre procedure will be developed to ensure the completeness of all reports submitted to Quality Assurance.

This will be discussed at a training program for Quality Assurance Specialists that will take place during the week of October 17th, 1994 as previously planned".

7.2.3 MB COMMENTS

Lack of adequate systems for error reporting and management was noted frequently during our inspections. The issue also was raised in our summary reports as being an indicator of a lack of understanding of GMP principles.

7.3.1 FDA CITATION

London 19-21 Sept 1994. Ms Sandra White (4 Citations)

#2 *Review of monthly apheresis collection set lot sheet records revealed that daily quantity/lot number entries were recorded in pencil*

7.3.2 CRC RESPONSE

"The corrective action was taken immediately and further entries were made in pen. Proper record keeping procedures will be reinforced at the next training session".

7.3.3 MB COMMENT

Minor GMP non compliance.

EDMONTON

There were 3 further citations at the Edmonton inspection (19-21 Sept 1994, 10 Citations, Mr Ronnie E Jackson) that were "QA" issues ie:

7.4.1 FDA CITATION

#7. *There are no written procedures covering corrective measures to be taken when component quality control results do not meet standards*

7.4.2 CRC RESPONSE

"A Centre Operation Procedure is now being developed to document measures taken when component quality control results do not meet standards".

7.4.3 MB COMMENT

This is a minor GMP non compliance.

7.5.1 FDA CITATION

#8. *Glycine Soja reagent (QC control check for insuring proper enzyme*

treatment of reagent Red Blood Cells) fails to bear an appropriate expiration date

7.5.2 CRC RESPONSE

"Immediate corrective action has been taken for future supplies. A replacement shipment is now in transit".

7.5.3 MB COMMENT

This is a minor GMP non compliance.

7.6.1 FDA CITATION

#10. Validation protocols covering installation and field check-out procedures of blood cell processing and storage equipment are not dated, and fail to show that they have been reviewed and/or approved prior to implementation

7.6.2 CRC RESPONSE

"Effective immediately, validation protocols covering installation and field check-out procedures of blood cell processing and storage equipment will be dated, and review and approval by appropriate management personnel will be documented prior to implementation".

7.6.3 MB COMMENTS

This an important issue but there is insufficient information on which to base any further qualification. We have raised lack of validation as a major matter of concern. This seems to suggest validation was done but inadequately documented.

7.7.1 FDA CITATION

#15. The National SOP CQ7000 is inadequate and contains conflicting statements. Definitions for "quarantine", "quarantine for destruction", and "on hold" are circuitous and unclear. Point 8.3 of pg 7 and point 9.2 on pg 8 contradicted each other regarding the "quarantine" of components

7.7.2 CRC RESPONSE

"National SOP CQ7000 will be revised to improve the clarity of definitions and instructions prior to application for licensure".

7.7.3 MB COMMENT

This is an important point. There must be clear rules on such matters.

7.8.1 FDA CITATION

Regina 29-30 Sept 1994. Ms Lisa Althar (13 Citations)

#2 There are no written procedures for calibration of the Disease Testing

7.8.2 CRC RESPONSE

"A Centre Operating Procedure for the calibration of the thermometers will be implemented within three weeks".

7.8.3 MB COMMENT

A minor GMP non compliance.

7.9.1 FDA CITATION

#8. *Written procedures (COP EQ 207) require temperature readings of the glass and digital thermometers, differing by greater than 2°C, to be repeated within 60 minutes, however, there is no documentation of the actual time readings are taken to ensure this is performed as required*

7.9.2 CRC RESPONSE

"Effective October 3, 1994 times of the readings will be recorded. New monthly recording charts will be developed and implemented by November 1994".

7.9.3 MB COMMENT

Minor GMP non compliance.

7.10.1 FDA CITATION

Regina 29-30 Sept 1994. Ms Lisa Althar (13 Citations)

#2. *Procedures used in centre operations are not always signed and dated as approved per procedure CQ1000. Procedures observed include Registrar Training and Incident Reporting*

7.10.2 CRC RESPONSE

"The Draft SOP in question will be removed from SOP binders and only signed approved versions will be placed in the binders in the future. All procedures will be signed and dated".

7.10.3 MB COMMENTS

This is a minor GMP non compliance.

8. GENERAL

8.1.1 FDA CITATION

Hamilton 19-22 Sept 1994. Ms Erin Hyer (38 Citations)

#39. *The job description for the Medical Director does not indicate that this position includes the role of responsible head accountable for daily operations of the facility*

8.1.2 CRC RESPONSE

"The job description of the Medical Director has always been interpreted to include accountability for daily operations of the facility. A revised job description has been developed and will be implemented prior to application for licensure".

8.1.3 MB COMMENT

Not a safety issue, a point of (GMP) detail.

ANNEX III



Report on the United States Food and Drug Administration Inspections

BY DR. H.H. GUNSON

EXECUTIVE SUMMARY

1. The introduction comprises the reasons for the requested report by The Honourable Mr. Justice Krever and the documents studied during the course of the preparation of the report.
2. Section 2 is an analysis of the regulatory system in the USA and the functions and powers of the Federal Drugs Administration (FDA).
 - 2.1 It is pointed out that recent trends in FDA activities have concentrated on Quality Assurance Management and Donor Selection.
 - 2.2 The FDA, as a regulatory body backed by legal enforcement, expects each registered/licensed facility to comply with the published regulations.
3. Section 3 contains comments on the criticisms contained in the FDA reports.
 - 3.1 These are categorised as:
 - 3.11 Matters of major concern
 - Training
 - Computer software
 - Procedures which require verification at a later date
 - L59 Coding of donors
 - Entry of deferral codes prior to review for accuracy
 - behaviour for HIV
 - 3.12 Matters of concern
 - Standard operating procedures
 - Non-compliance with manufacturer's instructions
 - Look-back procedures

- Error reporting
- Date of expiry
- Labelling donations for "Autologous use only"

3.13 Other matters

- Physical examination of apheresis donors
- Review of serum protein levels of apheresis donors
- Demonstration that the donor has a normal temperature
- Demonstration that the donor blood pressure is normal
- Preparation of the arms of donors prior to blood collection
- Quality control of copper sulphate solution
- Anti-HBc testing of blood donations

Each item in section 3 has been discussed and the reason for including them in each section is put forward.

1. INTRODUCTION

- 1.1 This report has been prepared at the request of The Honourable Mr. Justice H. Krever, Commissioner of the Inquiry on the Blood System in Canada.
- 1.2 The Food and Drug Administration (FDA) of the United States of America (USA) have inspected 12 of the 17 blood centres in Canada. The inspectors have provided reports which detail non-compliance with FDA standards. However, there is no indication in these reports of the priority or seriousness given to the matters of concern.
- 1.3 An attempt has been made in the report to categorise the adverse comments of the FDA inspectors into those which have a potentially serious effect on the quality and safety of products and those which may do so and those which exist principally for the protection of the donor.
- 1.4 The documents studied during the preparation of this report are:
 - 1.41 Summaries by the FDA inspectors noting matters of non-compliance and the responses of the following blood centres
 - Edmonton
 - Halifax
 - Hamilton
 - London
 - Regina
 - St. John
 - Lang's Cold Storage
 - Saskatoon
 - Sudbury
 - Toronto
 - Vancouver
 - Windsor
 - Winnipeg
 - 1.42 Transcripts of the testimony by the Directors of the Centres in Hamilton, London and Toronto.
 - 1.43 The Code of Federal Regulations, section 21, parts 600-799, revised 1st April 1993 and amendments to November 1994.

2. THE FOOD AND DRUG ADMINISTRATION (FDA)

- 2.1 Before discussing the specific comments concerning the practices at the blood centres it is helpful to consider how the FDA came into being and its responsibilities. These have been derived from a talk given by J.S. Epstein, an official of the FDA, in 1991. (1).
- 2.2 The USA has a long history of regulation for drugs and biologics beginning with the Virus, Serum and Toxins Act of 1902 and the Food and Drug Act of 1906. Following deaths due to contamination of Elixir of Sulphonamide the Federal Food, Drug and Cosmetic Act (FD&C) (1938) established the need for manufacturers to demonstrate drug safety before marketing. This act was amended in 1962 following the thalidomide tragedy in Europe to increase the assurance of safety and to require the demonstration of effectiveness of a drug. Provisions of the FD&C Act incorporated Good Manufacturing Practice (GMP) and requirements for registration and inspection.
- 2.3 In 1944 the Public Services (PHS) Act unified and codified the regulation of biologic products. Blood products were not specifically identified until an amendment to the PHS Act was passed in 1973.
- 2.4 In 1972 the jurisdiction for regulation of blood products was transferred from the National Institutes for Health to the FDA, and in 1976 the FDA published specific regulations governing blood and source plasma collection establishments. In addition in 1976, regulatory authority was extended to include safety and efficacy of medical devices.
- 2.5 The FDA has regulatory authority covering several areas concerning blood and blood products, viz:
 - Approvals (Establishment and product licensing)
 - Surveillance (Establishment registration and inspection, error and accident reports, product testing)
 - Enforcement (Regulatory actions)
 - Communications (Regulations, guidelines)
- 2.6 FDA regulation of the blood system in the USA operates through approval authorities related both to the establishments and the products. All blood collection establishments in the USA must register annually with the FDA and obtain a licence prior to the manufacture of products for interstate commerce. Both registered and licensed establishments must comply with the applicable regulations issued by the FDA.

In response to reports of errors and accidents or those found on inspection, the FDA can institute the recall of a product, and, dependent on the potential health hazard, may issue warning letters, suspend or revoke licences and can initiate court injunctions or criminal proceedings.

- 2.7 More recently, the FDA has concentrated on two areas of activity of blood centres.

2.71 Quality assurance management

Increased emphasis is now being placed on overall quality assurance to ensure accuracy, consistency, accountability and satisfactory operational control.

Quality assurance management is wide-ranging. It includes the methods for detecting and handling errors, inspections, regular audits, validation of automated, computer equipment and software and the provision of standard operating procedures (SOPs) which accurately reflect operational activities and comply with the regulation.

2.72 Donor selection

The safety of a blood product commences with the selection of the donor. Voluntary self-exclusion has become a valuable tool in reducing the risk of transfusion transmitted infections. However, this is one area where there is still much to be accomplished. Leitman et al (1989) (2) found that 80% of males and 60% of females seropositive for HIV had risk factors which should have led to self-exclusion.

One of the principle factors is to ensure that the donor can read and understand written leaflets and questions. Current trends are to question the donor verbally to ensure that he/she has no risk activities which may preclude donation.

2.8 CONCLUSION

- 2.81 It can be seen from the above that the FDA is a regulatory body with its regulations backed by legal enforcement.

2.82 It is not surprising that their reports following inspections are not ranked in order of seriousness. It is expected that registered and licensed facilities comply with all the regulations.

3. COMMENTS ON THE CRITICISMS CONTAINED IN THE FDA REPORTS

3.1 In this section I have attempted to give my personal views on the relative seriousness of the adverse comments made by the FDA inspectors following their visits to the 12 Transfusion Centres and Lang's Cold Storage.

In doing this I have born in mind that the aethos of the FDA regulations is to provide evidence that blood products meet prescribed standards of safety, purity and potency. Safety is a wide term but I interpret it to include quality and the assurance of quality.

3.2 In some instances equal weight may be given to more than one matter of concern and, therefore, I have attempted to place these in broad classifications.

3.3 MATTERS OF MAJOR CONCERN

3.31 Training

- There is evidence in the majority of the FDA reports of a lack of adequate training of Centre personnel.
- There are specific comments in some Centres to the inadequacy of training records for the computer system with no written procedures for training and training updates, for assessing training and its adequacy and for progression in the computer system. Also, training in the computer system is conducted in the "live" situation with active records.
- In two Centres there is no documentation that the Laboratory Manager/Computer Services Manager had received specialised training in laboratory equipment/operations they supervise.
- Other comments imply the lack of training in proper procedures, e.g. component labels are placed on the satellite bags prior to the completion of component preparation, the use of unapproved SOPs, personnel performing weekly volume verification of the Ortho Summit and personnel reviewing the Ortho Summit volume variation "... did not note values deviated from

manufacturer's specifications," the manufacturer's operators manual for the Ortho Summit requires the use of a direct-displacement pipette ".... It has not been determined that the Gilson Pipetman in use ... is a direct displacement pipette." Other examples can be found.

References

- (1) Epstein, J.S. (1991) Regulations and regulatory mechanisms related to transfusion medicine in the USA. *Tranfusion Medicine: Fact and Fiction*, Editors C.Th Smit Sibinga, P.C. Das and J.D. Cash.
- (2) Leitman et al (1989) Clinical implications of positive tests for antibodies to Human Immunodeficiency Virus Type 1 in asymptomatic blood donors. *N.E.J. Med.* 321, 917-24.

One of the major factors in achieving a high quality blood supply is to have in place an organised, documented training programme combined with supervision to ensure that specified operations are undertaken in accordance with the training and operating procedures.

3.32 Computer software

- It is evident from the reports that the existing computer system is inadequate. This is confirmed by the evidence given by Dr. Blajchman "... we have tried very hard within the Red Cross to use bandaids and chewing gum, as it were, to sort of make the system suffice."

Also, there has been a computer malfunction at the London Centre, which makes it difficult to understand why at least some Centres do not have written instructions for a manual back-up in the case of computer failure.

- Specifically, the present computer system does not permit the identification and correction of duplicate donor records. It is important that this is achieved. If a donor presents at one Centre and is deferred it is important that this information is available to another Centre he/she may attend in the future.

Great reliance is now placed on Computers for verification and validation of test results, for release of products, for determining the source of a product and for information regarding its issue in the event of a recall. I understand that the system is currently being enhanced and priority should be given to this.

3.33 Performing procedures which require verification at a later date

- 3.33.1 - Allocation of a donation number at a blood collection session. This has been described as a rudimentary test by the FDA inspectors. Dr. Roslyn Herst, stated in her evidence that for first time donors "... an admittedly crude rapid ABO group right at the front end of the clinic (is performed) and that is one of the two tests that is done from the finger stick blood." This is done in less than ideal conditions. "... This is done with whatever drop they can get out of the finger ... under inadequate lighting conditions ... they have to look and see if there is clumping or if there is no

clumping. They may, if the reagents are slow reacting, not give sufficient time so that instead of being group AB the reaction comes up and looks like its an A, but they have handed them an AB label and it goes through." In Toronto this results from this testing led to an error rate of approximately 1 in 500 donations.

- For donors who have given blood previously the group recorded at the last donation is used to determine the donation number.
- There is a complex procedure for correcting wrong groups which involves 29 steps (according to the procedure detailed by the Toronto Centre). It involves nursing, laboratory and computer staff. It can apply also to autologous donations.

The potential for human error in both transcribing and testing during this correction process is considerable. When this is combined with an inadequate computer system it becomes even more undesirable.

- Dr. Blajchman, in his evidence, stated that there is a check if the donor has given before and one from the screening test for a new donor and finally the definitive test. "In the American system there is only the two and in one instance, the instance where its a new donor, its only one test."

The FDA regulations state (paragraph 640.5) "At least two blood group tests shall be made and the unit shall not be issued until grouping tests by different methods or with different lots of antisera are in agreement."

I can appreciate that it is undesirable for donation numbers to repeat in too short a time period. However, it is important that a more secure method for achieving this is devised rather than the present system of incorporating the ABO group in the donation number.

3.33.2 L59 Coding of donors

- This code allows donors to continue to donate although there are indications that they should have been deferred.

Collecting blood from these donors and subsequently discarding it, raises ethical issues. Also, it is yet another instance where there is a potential for human error in that the donation has to be withdrawn. If all the tests on this donation are satisfactory the donation may proceed incorrectly to release.

If there is good evidence at the blood collection session that the donor has not been truthful or there are reasons why he/she should not be bled then, however difficult it may be, the donor should be deferred.

3.33.3 Entry of deferral codes prior to review for accuracy or appropriateness

- In this instance a nurse applies a deferral code before there is a review to determine its accuracy. Dr. Blajchman in his evidence stated that a check took place eventually but did not give a time scale. The review was undertaken by the Nursing Supervisor and the Computer Services Manager.
- When challenged that a person may be deferred for six months when they should have been deferred for one year and could donate again when they ought to have been deferred, Dr. Blajchman accepted that this was the theory behind the safety argument.

I consider this to be unacceptable practice. In my view donor deferral should be carried out by a Medical Practitioner rather than a Nursing Supervisor and a Computer Services Manager. Furthermore, the reason for the deferral should be confirmed before an entry is made on the computer records.

3.34 Verbal questioning concerning risk behaviour for HIV infection

- There is concern in many countries that some donors cannot understand the written word. This was exemplified in Dr. Herst's testimony in that, in Toronto, they had to cope with donors who may not understand English or French.

Dr. Mayo's research for NIH did show that there was an increased incidence of deferral for HIV risk activities when donors were given verbal questioning. Although this technique is not foolproof since the donor may not answer the questions truthfully, it does, at least, afford the opportunity to assess the capability of the donor to

understand the language of the written questionnaire. In the U.K. we are progressing towards verbal questioning of the donor for the reasons stated above.

If the confidential unit exclusion form is not completed the unit has to be withdrawn and this is yet another example of the potential hazard for human error.

3.4 MATTERS OF CONCERN

3.41 I have ranked the following as less important from the aspect of safety of the blood product, although they may contribute towards this.

3.42 Standard Operating Procedures (SOPs)

- It is evident from the reports that there is a serious lack of SOPs. I noted that there were more than 15 operational procedures which were not covered by an appropriate SOP in addition to those concerning training about which I have commented already.
- In some instances the National SOP did not accurately reflect the equipment in use at all Centres, there were no written procedures to define access authorisations to a programme in the computer, the failure to identify/indicate the known standard weight which insures blood containers are filled with the proper amount of blood (in some instances these were different from the range of parameters allowed by the manufacturer).
- There are several examples stated of non compliance with existing SOPs.

SOPs are an important part of Good Manufacturing Practice. They provide a documented record of operational procedures and should be updated as changes occur or lessons are learnt from errors which have occurred.

I was surprised to note the number of National SOPs. Whilst it is desirable to achieve operational standardisation, it may not be possible for geographical and demographical reasons to achieve complete uniformity in each Centre. The authors of SOPs should be those working in the Centres (with the possible exception of the SOP for the use of the computer if this is a national computer programme). National agreement to the contents of the SOP to ensure that the end result does not materially differ in the Centres should be obligatory. Thus, the National Headquarters should provide co-ordination and leadership.

3.43 Non-compliance with manufacturer's instructions

- There are several examples of this, the most frequent being the inclusion of a "mix mode" in HBsAg testing during the 37°C incubation step. It is claimed that this method has been proven to increase the sensitivity of the assay and has been accepted by the Canadian regulatory agency.

I do not know whether Canada has laws governing product liability. In the U.K., variations from the manufacturer's product insert would transfer liability from the manufacturer to the user if there was a false negative in the test.

3.44 Look-back procedures

- In the FDA report on the Hamilton Blood Centre, it is stated that only a 70 day previous donor inventory retrieval is done for units from donors testing repeatedly reactive for HBsAg. The fact that this had been changed to six months in 1992 and the update had not been inserted into the Hamilton SOP prior to the inspection in 1994 is a serious matter.

Whilst six months is probably adequate for Hepatitis B it should be noted that the FDA are proposing to modify their regulations with respect to donors who test as anti-HIV positive but who have, in the past, been seronegative for HIV (including HIV-1 and HIV-2). This proposal requires that a donor who previously donated blood subsequently is tested for HIV and the tests found repeatedly reactive, the blood establishment shall perform a more specific test and notify consignees who received such blood so that appropriate action is taken. Blood establishments and consignees would also be required to quarantine previously collected blood and blood components from such donors. Some products have expiration times greater than six months (e.g. fresh frozen plasma)

Indeed, under the proposed regulation 610.46 there will be a requirement to quarantine units collected from the donor within the past five years if intended for transfusion and within the past six months if intended for further manufacture.

- There are adverse comments by the FDA inspectors on inadequacies in quarantine arrangements, although some (e.g. Toronto) are excellent. The procedures which need to be taken require discipline by the staff concerned and in some instances will require investment for new cold-stores.

The look-back of previous donations is an important aspect, although it is recognised that without adequately computerised records this can be a time-consuming procedure. FDA have proposed that products are quarantined on discovery of HIV seroconversion of the donor and released only after a negative result in the more specific test which should be available within a two week period. A revised SOP for this procedure will be required.

This matter does affect the safety of the product since some of the products from previous donations may have been tested within the "window" period, i.e. the donor is infected with HIV but is negative for anti-HIV. It is material, however, for the health of the patient.

3.45 Error Reporting

- There seems to be some confusion (particularly at the Hamilton Centre) about which errors should be notified to the Central Office and those which should not.

This matter should be clarified by the National Office.

3.46 Date of Expiry

- There are several comments concerning the absence of the date of expiry on products.

Whilst it is true that the majority of hospital staff will be aware of the length of time that a product can be used from the date of collection, it is prudent to include the date of expiry on the label.

Source plasma derived from plasmapheresis requires by FDA regulations an expiry date to be entered. I am not so sure that recovered plasma does not as stated in the responses by the National Office on several occasions. In section 610.5 of the Code of Federal Regulations, paragraph (c), there is a table of dating periods. In this table fresh frozen plasma has a dating period of one year from the date of collection if stored at -18°C or colder. (This plasma is separated from whole blood in less than six hours after collection). Plasma (which I consider includes recovered plasma, section 640.30) has a dating period of five years from the date of collection if stored at -18°C or colder.

The statement of the expiry date on the label is a measure which reduces the potential for human error.

3.47 Labelling donations for "Autologous use only"

- Criticism was raised about the lack of this label on autologous donations when the donors did not meet the normal criteria for acceptance.

Although autologous blood is no longer shipped to the USA, it is essential that an autologous donation which is obtained from a donor who does not meet the usual criteria for acceptance is labelled accordingly.

This is done to ensure that the blood/blood product is only transfused to the donor. The guidelines for autologous donations need not be identical to those for homologous donations.

3.48 Lang's Cold Storage

It is difficult to understand details of the contractual arrangements between Lang's Cold Storage and the National Office.

There appears little doubt from the FDA report that a firmer control should be placed on Lang with respect to record keeping.

3.5 OTHER MATTERS

- 3.51 In this section I have compiled those adverse remarks which contribute more to the safety of the health of the donor rather than the product and surrogate testing of the blood donation, although it does include a section on anti-HBc testing of donor blood.

3.52 Physical examination of apheresis donors

- several Centres were criticised for either not performing a physical examination on donors entering an apheresis programme, at twelve monthly intervals thereafter or that these examinations were not performed by a qualified physician.

These examinations may reveal the unsuitability of a donor to donate blood because of the potential danger of transmitting an infection. However, the primary value is to protect the health of a donor entering an apheresis programme where the attendance is more frequent than donating whole blood. The donor is entitled to have this examination performed by a qualified physician.

3.53 Review of serum protein levels

Apheresis donors are required, by FDA regulations, section 600.65 paragraph b (1), to have a total serum plasma protein determination and a plasma or serum protein electrophoresis or quantitative immunodiffusion test (or equivalent) test to determine immunoglobulin composition of the plasma or serum. The results of these tests have to be reviewed by a qualified licensed physician and if the protein composition is not within normal limits or if the total protein is less than 6.0 g per 100 ml the donor shall be removed from the programme until these levels return to normal.

These are sensible precautions for the donor's health.

3.54 "The donor shall have a normal temperature"

I am sympathetic to the comments of your Medical Directors that if a donor had a raised temperature he/she would feel unwell and would be flushed and shivering.

To obtain an FDA licence, presumably, the temperature of the donor will have to be taken at the time of donation.

3.55 Demonstration that the systolic and diastolic blood pressures are within normal limits

- There were several adverse comments that blood pressure tests were not undertaken.

There is no doubt that attendance at a blood collection session can result in an increase in the systolic blood pressure due to nervousness or anxiety. However, taking the blood pressure of donors is worthwhile as a public health measure. If the diastolic pressure is greater than 100 mm mercury then the donor may require medical treatment. With respect to the systolic pressure, the examining physician has the ability to decide whether the donor can donate blood (Federal code of regulations, section 640.3 paragraph b(2) and section 640.60 paragraph c (2)).

3.56 Arm procedures do not include a method and duration of a scrub technique for 30 seconds

The FDA regulations prescribe that "The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully that gives maximum assurance of a sterile container of blood. (Federal code of Regulations, section 640.3 paragraph (f) and 640.64 paragraph (e)). There is no mention of a time period.

Providing the technique used for arm cleansing prior to donation has been validated for safety it should comply with the FDA requirements.

3.57 Quality control of the copper sulphate test for the determination of haemoglobin

- Several Centres were criticised for not performing a quality control test on the copper sulphate solutions used to screen donors for haemoglobin level.

There is a valid argument that if a test is being performed then it should be performed properly. To do this it is necessary to quality control the specific gravity of the copper sulphate solution used at blood collection sessions.

I cannot agree with Dr. Blajchman's testimony that this is a matter of little importance. If the copper sulphate solutions are left exposed to the air for long periods then some evaporation will take place and there may be concentration of the copper sulphate. This can result in donors being falsely rejected. If he is correct that the solution was changed after every six donors this should not occur unless the session was poorly attended.

The opened containers in which the copper sulphate is used should not be exposed to the atmosphere for more than about 30 minutes.

Donors who are rejected for a low haemoglobin value often do not return. Also, they may be worried that they have a serious illness such as leukaemia. It is important that if this test is used, it is properly controlled.

3.58 Anti-Hbc testing of blood donations

- There are several adverse comments that anti-HBc testing of donations is not carried out.

I have left this item until last because it is controversial. Anti-HBc testing of all donations in the USA was introduced in the late 1980s as a surrogate marker for non A, non B hepatitis and also as a life-style marker since there are persons who are HBsAg negative but anti-HBc positive.

Since Hepatitis B is sexually transmitted, persons who are positive for anti-HBc may be prone to other sexually transmitted diseases. The introduction of anti-HCV testing of all blood donations has largely eliminated its value as a surrogate marker. It is still a useful test to perform if there is doubt that the HBsAg test is positive and I

understand that it is used as such by the National Reference Laboratory in Canada.

Anti-HBc testing is not required in the Code of Federal Regulations and I am at a loss to explain why the FDA inspectors made these comments.

ANNEX IV



Report on the Bureau of Biologics Inspections

BY MARTIN BRUCE

RESPONSE TO QUESTIONS POSED BY COMMISSION COUNSEL

1. **CONTEXT OF THE RESPONSE**

This response principally deals with BoB inspection guidelines and reports. The general context that was defined in my 25 November 1994 response on the FDA inspection reports also is applicable here. However, it must be acknowledged that comparing FDA, BoB and the international team's reports is even more difficult eg BoB reports generally suggested a broader scope than did FDA reports; BoB inspections generally had 4 auditors, FDA had one.

Furthermore, it must again be emphasised that each inspection reviews only selected elements of the system and the number of elements selected will be influenced by the audit scope. Generally, inspections that determine whether a licence should be issued or renewed will have a broader scope than will a regular 'monitoring' inspection.

From the inspection reports it appears that the BoB audits had a broad, regulatory type approach. As suggested in my response of 25 Nov 1994, the scope of the FDA inspections seemed to vary between inspectors and between Centres. The scope of inspections undertaken by the international team was consistently broad and in-depth in order to satisfy the remit.

2. **PART II**

2.1 *Are the principal and other major areas of concern identified by the international inspection team covered by the BoB inspection guidelines?*

Yes, these guidelines do cover the matters of concern raised in our inspections. However it must be understood that they provide merely a generic framework for inspections.

It seems reasonable to suggest that the interpretation of such guidelines will be influenced by the inspectors' knowledge of the field of work being inspected and of the type of inspection being planned. These matters of interpretation could be illustrated by using an example. Computer systems are not mentioned explicitly but if the inspector knew or established that computerised systems were an important part of the overall systems then it would be appropriate to include them within the plan of a regulatory type inspection.

2.2 *Were the principal and other major areas of concern identified by the international inspection team identified in the 1994 BoB inspections of these Centres?*

2.2.1 **Approach Taken**

A summary of the "principal" and other "major" matters of concern recorded by the international inspection team is given in appendix 1. These are numbered for easy

reference and are abbreviated from the original. This appendix indicates whether or not the BoB inspections for these sites identified the problems recorded by the international team. If the BoB reports suggest the area has been partially covered, this is shown. Also, after the BoB inspections were complete, Dr Boucher (BoB) wrote to Dr Aye (National Director) to indicate problem areas that were common to all Centres. For interest, this list has been included in this summary and in the analysis shown in appendix 1.

Finally, for completion, appendix 1 also indicates if FDA inspectors reported similar matters of concern to those cited as "principal" and "major" by the international team.

In appendix 2, where the BoB reports describe problems that were included in the international team's listing of "principal" and other "major" matters of concern, these are shown and commented on as appropriate.

2.2.2 Summary Of The Analysis

1. MONTREAL

In the Montreal inspection, the international team recorded 8 "principal" and 7 other "major" matters of concern. Of these 15 citations, the BoB report partially addressed 1 "principal" and 2 "major" concerns.

The "principal" concern related to inadequate arrangements for the provision of an effective, 24 hour system for handling product recalls. (The international team reported numerous additional concerns).

Of the two "major" concerns, one related to the failure to account for and destroy blood grouping labels on clinics, the other was a reference to inadequate arrangements to review and approve calibration and validation reports. These partially expressed the more extensive concerns reported by the international team.

2. SAINT JOHN

The international team recorded 10 "principal" and 9 other "major" matters of concern in the Saint John inspection. None of these were recorded in the BoB inspection report.

3. WINNIPEG

The international team identified 17 "principal" and 7 other "major" matters of concern in the Winnipeg Centre. One of the "major" concerns was partially addressed in the BoB inspection report ie the validation and calibration of equipment/instrumentation.

4. SYSTEM WIDE PROBLEMS

34 different and important problems were recorded by the international team. Of these, 22 were assessed as "principal" and 12 as other "major" matters of concern. Four of these 34 were included in the BoB assessment of system wide problems. (Correspondence Boucher - Aye 17 February 1994).

Of these 4, three partially addressed "principal" concerns reported by the international team, ie inadequate Centre arrangements/resources for QA; inadequate arrangements at Centres for product recalls, and inadequate Centre arrangements for the timely and effective implementation of National Procedures.

The remaining reported system-wide problem partially addressed the international team's concerns about lack of validation.

2.3 Are the FDA citations, which were considered (by M Bruce) to be "principal" and "major", covered by the BoB inspection guidelines?

The response to Part I questions show that only a few of the FDA citations were considered to be in the "principal" and "major" categories. Two of those classed as "principal" were the result of differences between Canadian and US Regulations. (ie inventory lookback for repeat reactive anti-HIV donors and close out of traceback procedures once a "positive" donor is found).

Of the others, 2 were classed as "principal"

- no expiry date on products
- the same donor could have a different registration number in different Centres (potentially, this could cause difficulty in deferral/lookback).

Multiple problems with the BLIS computer system were cited in the FDA reports. Collectively these were considered as a "principal" matter of concern but were not cited in BoB reports.

Finally, there were two FDA citations that were classed as "major"; one related to confirmatory testing for HBsAg, the other dealt with health assessment questionnaires.

All of these matters are covered in the BoB inspection guidelines, only the last one was reported (in part) at the BoB inspections.

RESPONSE TO QUESTIONS POSED BY COUNSEL, PART II

APPENDIX 2

ANALYSIS OF PRINCIPAL AND OTHER MAJOR MATTERS
OF CONCERN REPORTED BY THE INTERNATIONAL TEAM
VS BOB INSPECTION REPORTS

1. Montreal

1.1 i. International team ref appendix 1 #15

"Excess donation numbers are attached to the primary blood pack and are used in a variety of applications."

ii. BoB ref nursing #2

"Strict reconciliation of all Blood Collection bags and blood grouping labels is required, including those which are destroyed. Further, labels are to be defaced before being destroyed."

iii. MB Comment

These citations are not directly comparable, nevertheless they enunciate the same principal. Also, it may be implied that the BoB citation reflects some of our concern reported in the Saint John inspection. (ie appendix 1 ref #17, Saint John, "on clinics, "missing" blood group donation numbers were retrieved from waste containers and stuck on the relevant pack.")

1.2 i. International Team ref appendix 1 #9

"There was a general lack of manufacturing records for component processing and a lack of validation of plasma freezing and thawing processes."

ii. BoB ref Laboratories/Equipment #5

"Results of calibration and validation procedures should be reviewed and initialled by the Senior Technician, the Laboratory Manager or the QA Manager."

iii. MB Comment

It is not clear from the BoB citation whether they are referring to equipment,

processes or both. Also, I feel the review process recommended lacks an adequate structure.

- 1.3 i. International Team ref appendix 1 #

"Arrangements for product withdrawal and recall were inadequate."

- ii. BoB ref page 3 (no ref number on my copy)

"To effect recall procedures, a system must be implemented to ensure that a responsible person can be reached at all times."

- iii. MB Comment

The BoB team have recorded one of the various concerns we expressed in this area.

2. **Saint John**

None of the principal or other major matters of concern (respectively 10 and 9 in number) identified by the international team were reported by the BoB team.

3. **Winnipeg**

- i. International Team ref appendix 1 #9

"There was a general lack of manufacturing records for component processing and a lack of validation of freezing and thawing processes."

- ii. BoB ref Equipment/Instrumentation page 3

"A program of regularly validating and calibrating equipment used in areas of blood collection, processing, testing, storage and issuing is required. Centre staff should also perform calibration procedures following maintenance and service calls to ensure the equipment functions properly for the users." (continues)

- iii. MB Comments

This addresses part of the concern expressed by us. However, process validation is equally important (as is equipment validation)

4. **General**

4.1 The following were included in a listing of general points that arose from the 1994 BoB inspections. These were communicated from Dr Boucher (then BoB) to Dr Aye, (National Director) on February 17, 1994.

4.2.i. International Team ref appendix 1 #20

"Personnel arrangements/responsibility/authority for QA do not meet the standards needed to operate within a system of GMP."

4.2.ii. BoB Guidance ref correspondence, item 1

"The Quality Assurance department must be a distinct organisational unit that functions and reports to management independently of any other functional unit. As the Medical Director is responsible for the manufacturing, and, to ensure the independence required for this department, it is recommended that the quality assurance programme in each Centre report directly to the Head Quality Assurance or the National Director at the National Office in Ottawa." (continues)

4.2.iii. MB Comments

The BoB guidance partly articulates our concerns, however, I disagree with the notion that Centre QA Managers should report to an individual in the National Office. Every organisation, no matter how large must ultimately have someone who is responsible for manufacturing and quality. A much better solution would be to make the Centre Directors such a person (and have the QA Manager report to the Centre Director).

4.3.i. International Team ref appendix 1, #3

"Arrangements for product withdrawal and recall were inadequate."

4.3.ii. BoB Guidance ref Correspondence, item #3

"As part of the SOP for recall procedures, it is required that a Senior Manager be identified who could immediately initiate product recall procedures during non-working hours."

4.3.iii. MB Comments

This addresses one (arguably two) of the major comments raised by the international team ie the need to have 24 hour cover and that this should be part of the National SOP. However, it fails to identify other important points eg lack of documentation (from National) to ensure the consistent recording

of the recall event at the local Centre; lack of local SOPs for recalling blood components; need for a review in the National SOP for recall; National not following their recall SOP.

4.4.i. International Team ref appendix 1 #9

"There was a general lack of manufacturing records for component processing and a lack of validation of freezing and thawing processes."

4.4.ii. BoB Guidelines ref Correspondence, item #4

"Although some centres have validation/calibration programmes in place, immediate attention is required to ensure that outside contractors hired to perform such a validation/calibration perform these functions according to the Food and Drug Regulations and your SOP's. The documented method employed by the Contractor also need to be available."

4.4.iii. MB Comments

This addresses part of the concerns expressed by us. It is not clear whether the guidance refers to equipment, processes or both.

4.5.i. International Team ref appendix 1 #2

"The issue of SOPs and directives from National Office is causing serious problems for centres."

4.5.ii. BoB Guidance ref Correspondence, item #9

"Most centres do not have up to date Centre Operating Procedures (COP's) in place which are consistent with the most current National SOP."

4.5.iii. MB Comment

This confirms one of the various concerns we identified in this area.

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RESPONSE TO COUNSEL QUESTION

"Were the principal and other major matters of concern reported by the international inspection team identified in the 1994 BoB inspections of these Centres?"

P = "principal"; M = "major"

	International Team					BoB				FDA		
	Montreal (M)	Saint John (SJ)		Winnipeg (W)		M	SJ	W	Gen	SJ	W	Other 10 Centres
	# ref	# ref	# ref	# ref	# ref							
1	P	1.1	M	1.2.5	P	1.1.3	No	No	No	No	No	No
2	P	1.2	P	1.1.7	P	1.1.8	?	No	Part	No	No	Part, Toronto #14, Halifax #10
3	P	1.3	P	1.1.6	P	1.1.11	Part	No	Part	No	No	No
4	P	1.4	P	1.1.9	P	1.1.16	No	No	No	Yes	Yes	Yes (multiple) except Sudbury, Windsor, Winnipeg
5	P	1.5	P	1.1.8	P	1.1.15	No	No	No	No	No	No
6	P	1.6	-	-	-	-	No	No	No	No	No	No
7	P	1.7	P	1.1.10	P	1.1.17	No	No	No	No	No	Yes, Toronto #5, Hamilton #20
8	P	1.8	-	-	-	-	No	No	No	No	No	No
9	M	1.9	M	1.2.3 (and 1.2.4)	M	1.2.4	Part	Part	Part	No	No	Part, Edmonton #10, Vancouver #3 & #4
10	M	1.10	-	-	-	-	No	No	No	No	No	No

RESPONSE TO COUNSEL QUESTION

"Were the principal and other major matters of concern reported by the international inspection team identified in the 1994 BoB inspections of these Centres?"

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		International Team				BoB				FDA					
		Montreal (M)		Saint John (SJ)		Winnipeg (W)		# ref	M	SJ	W	Gen	SJ	W	Other 10 Centres
		# ref		# ref		# ref									
	P = "principal"; M = "major" * = expressors in Winnipeg were showing early signs of corrosion, ref #16														
11	There was no positive identification of the donor prior to venepuncture.	M	1.11	M	1.2.2	M	1.2.3		No	No	No	No	No	No	No
12	Procedures for reporting audits (BoB) do not lend themselves to timely corrective action.	M	1.12	-		-			No	No	No	No	No	No	No
13	The ABO and Rh (D) group of new donors is only tested once (for manual and automated procedures).	M	1.13	M	1.2.8	M	1.2.7		No	No	No	No	No	No	No
14	Arrangements for assuring the bacteriological safety of the cryo bath were inadequate.	M	1.14	M	(1.2.4)	-			No	No	No	No	No	No	No
15	Excess donation numbers are attached to the primary blood pack and are used in a variety of applications.	M	1.15	M	1.2.7	P	1.1.1		No	No	No	No	No	No	No
16	Plasma expressors were badly corroded (pitted) and had the potential to cause pinhole leaks in blood packs.	-		P	1.1.1	*			No	No	No	No	No	No	No
17	The automated blood grouping system did not measure up to current standards, did not allow for positive sample ID and the sequential numbering equipment malfunctioned.	-		P	1.1.2	-			No	No	No	No	No	No	No
18	On clinics, "missing" blood group/donation numbers were retrieved from waste containers and stuck on the relevant pack.	-		P	1.1.3	-			Part	No	No	No	No	No	No
19	Controlled temperature storage and, especially, arrangements for alarm systems were inadequate.	-		P	1.1.4	P	1.1.6		No	No	No	No	No	No	No

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RESPONSE TO COUNSEL QUESTION

"Were the principal and other major matters of concern reported by the international inspection team identified in the 1994 BoB inspections of these Centres?"

P = "principal"; M = "major"

* recorded and raised at inspection, added to final report for info after wrap-up meeting

	International Team				BoB				FDA		
	Montreal (M)	Saint John (SJ)		Winnipeg (W)	M	SJ	W	Gen	SJ	W	Other 10
	# ref	# ref	# ref								
20	-	P	1.1.5	P	1.1.9	No	No	Part	No	No	No
21	-	M	1.2.1	-	-	No	No	No	No	No	No
22	-	M	1.2.6	-	-	No	No	No	No	No	No
23	-	M	1.2.9	P	1.1.13	No	No	No	No	No	No
24	-	M	* -	P	1.1.4	No	No	No	No	Yes	Yes, Toronto #3, Edmonton #4, Hamilton #19
25	-	-	-	P	1.1.2	No	No	No	No	No	No
26	-	-	-	P	1.1.5	No	No	No	No	No	No
27	-	-	-	P	1.1.7	No	No	No	No	No	No
28	-	-	-	P	1.1.10	No	No	Part	No	No	Part
29	-	-	-	P	1.1.12	No	No	No	No	No	Part, Vancouver #2
30	-	-	-	P	1.1.14	No	No	No	No	No	No

Personnel arrangements/responsibilities/authority for QA do not meet the standards needed to operate with a system of GMP.

Inadequate checking of TD confirmatory result entry to BLIS.

Inadequate validation of and arrangements for red cell antibody screening.

Health and Safety concerns.

Blood components carry only a collection date, not an expiry date as notified in the CRC Circular of Information for the use of Human Blood and Blood Components Feb 1994.

Premises not of an adequate standard to permit manufacturing in compliance with GMP.

Therapeutic products (albumin, Pentaspan) stored in poorly controlled conditions outwith their notified storage temperature.

Inappropriate arrangements for the storage of general supplies.

There was no adequate controlled document system.

There was evidence that despite double checking, a third check revealed a large number of health check questionnaires were not completed.

"Therapeutic plasma" untested and with no known history stored in an uncontrolled environment.

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RESPONSE TO COUNSEL QUESTION

"Were the principal and other major matters of concern reported by the international inspection team identified in the 1994 BoB inspections of these Centres?"

P = "principal"; M = "major"

	International Team				BoB				FDA		
	Montreal (M)		Saint John (SJ)		Winnipeg (W)		# ref	M	SJ	W	Other 10 Centres
	# ref		# ref		# ref						
31	-		-		M	1.2.1		No	No	No	No
32	-		-		M	1.2.2	Part	No	No*	No*	No*
33	-		-		M	1.2.5		No	No	No	No
34	-		-		M	1.2.6		No	No	No	No

* this excludes reference to FDA citations on donor temperature, pulse and arm examinations

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